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SUPER ARDUA

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P, 25,397

6 reasons why more doctors prescribe Prempak-C and Premarin than any other HRT.

50 YEARS EXPERIENCE

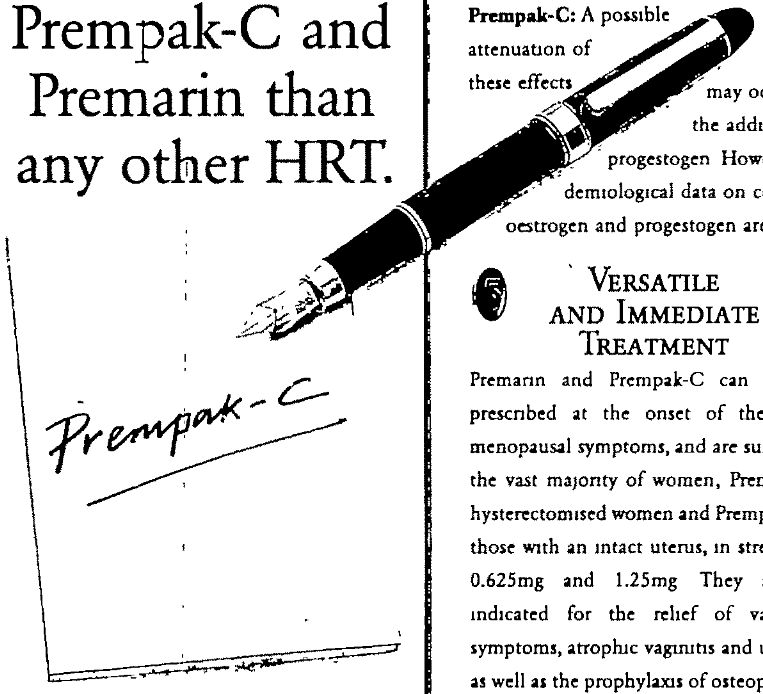
Premarin, a natural conjugated oestrogen, which is also used in the formulation of Prempak-C, is the only oestrogen used in any HRT with 50 years experience. The majority of long term studies, therefore, relate to the conjugated oestrogen found only in these products

LONG TERM SAFETY - BREAST CANCER?

Both doctors and patients are justifiably concerned about the potential risks of breast cancer for women taking HRT. Whilst there is suggestive evidence of a small increased risk of breast cancer with long-term HRT (greater than 5 years), this varies with the type and dose of the oestrogen used However, a recent comprehensive review of 31 studies provides evidence that menopausal therapy consisting of 0 625mg/day of conjugated oestrogens does not increase the risk of breast cancer [1] Most studies, in fact, relate to conjugated oestrogen and so there is insufficient data to arrive at similar conclusions for any other regimen

PROPHYLAXIS OF OSTEOPOROSIS

Prempak-C and Premarin are both indicated for the prophylaxis of osteoporosis in women at risk of developing fractures. A minimum daily dose of 0 625mg Premarin preserves bone mass, therefore reducing the risk of debilitating injuries such as hip fractures, by up to 66%.[2,3] Further estimates suggest that prescribing Premarin for at least 10 years will reduce the risk of mortality linked to osteoporosis by 60% [4]



REDUCING CARDIOVASCULAR DISEASE RISKS

Premarin: A recent review of considerable epidemiological evidence has shown, overa a 50% reduction in risk of coronary disea in oestrogen users The most common fo of oestrogen used in all these studies v conjugated oestrogen, i.e. Premarin

Prempak-C: A possible attenuation of these effects may occur with the addition of progestogen However, epidemiological data on combine oestrogen and progestogen are limite

VERSATILE AND IMMEDIATE TREATMENT

Premarin and Prempak-C can both be prescribed at the onset of the earlies menopausal symptoms, and are suitable f the vast majority of women, Premarin f hysterectomised women and Prempak-C f those with an intact uterus, in strengths o 0.625mg and 1.25mg They are also indicated for the relief of vasomotor symptoms, atrophic vaginitis and urethritis, as well as the prophylaxis of osteoporosis in women at risk

COST EFFECTIVE

Treatment costs are becoming increasingly important, especially as long term therapy can last from 5 to 10 years or longe Compared to other forms of HRT, Wyeth' products cost remarkably little; Prema costs just £1.84 and Prempak-C costs £4 for 28 days of therapy [7]

PREMPAK-C
PREMARIN

ABBREVIATED PRESCRIBING INFORMATION

PREMARIN **USES:** Menopausal and post menopausal oestrogen therapy in women without a uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures

DOSAGE AND ADMINISTRATION: Natural conjugated oestrogens 0 625mg - 1.25mg daily Continuous administration is recommended. In women with an intact uterus the addition of a progestogen for 10-12 days per cycle is essential

CONTRA-INDICATIONS: Known or suspected pregnancy and during lactation History of known or suspected cancer of the breast Oestrogen dependent neoplasia Undiagnosed abnormal genital bleeding Active thrombophlebitis or thromboembolic disorders Acute or chronic liver disease. Rotor or Dubin-Johnson syndrome Severe cardiac or renal disease

WARNINGS AND PRECAUTIONS Some studies have reported a small increased risk of breast cancer in long term oestrogen replacement therapy users (greater than 5 years), others however have not shown this relationship It is not known whether concurrent progestogen influences this risk The risk of endometrial hyperplasia and carcinoma with unopposed oestrogen use is lowered by the addition of a progestogen Diseases that may deteriorate during therapy include otosclerosis, multiple sclerosis, systemic lupus erythematosis, porphyria, melanoma, epilepsy, migraine and asthma Use with caution in patients with pre-existing uterine fibroids, endometriosis, breast nodules, fibrocystic disease, and in those with a history of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, cardiac or renal dysfunction Discontinue if jaundice, migraine, visual disturbances, thromboembolic phenomena or significant hypertension develop Certain endocrine and liver function tests may be affected Rarely idiosyncratic hypertension may occur Discontinue treatment prior to surgery or prolonged immobilisation Gallbladder disease Insulin requirements may be altered Premarin is not an oral contraceptive

SIDE EFFECTS The following have been reported with oestrogen therapy premenstrual-like syndrome, increase in size of uterine fibromyomata, vaginal candidiasis, changes in cervical erosion and secretion, cystitis-like syndrome, breast changes, gastrointes symptoms, chloasma, melasma, erythema multiforme, erythema nodosum, haemorrhagic erupti alopecia, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headache migraine, dizziness, mental depression, chorea, weight changes, reduced carbohydrate tolerance, aggravation of porphyria, oedema, changes in libido, leg cramps

PRODUCT LICENCE NUMBERS Premarin 0 625mg PL0011/0165 Premarin 1 25mg PL0011/0166 Premarin 2 5mg PL0011/0167 **BASIC NHS PRICE:** Premarin 0 625mg £1 84 (28 days) For full prescribing information please refer to data sheet

PREMPAK-C **USES** Menopausal and postmenopausal oestrogen therapy for women with a intact uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures

DOSAGE AND ADMINISTRATION Natural conjugated oestrogens 0 625mg - 1 25mg daily and one norgestrel 0 15mg tablet should be taken daily from day 17 to day 28 of oestrogen therapy

CONTRA-INDICATIONS As for Premarin

WARNINGS AND PRECAUTIONS: As for Premarin Prempak-C is not an oral contraceptive

SIDE EFFECTS As for Premarin Breakthrough bleeding and spotting Change in menstrual flow, dysmenorrhoea, amenorrhoea

PRODUCT LICENCE NUMBERS: Prempak-C 0 625mg PL0011/0161 Prempak-C 1 25mg PL0011/0162

BASIC NHS PRICE: £4 06 - 28 days For full prescribing information please refer to data sheet

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PREMARIN*
(Conjugated Oestrogens)

Wyeth Laboratories, Huntercombe Lane South,
Taplow, Maidenhead, Berkshire SL6 0PH.

PREMPAK-C*
(Conjugated Oestrogens + Norgestrel)

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[1] Altman, D. G., Gore, S. M., Gardner, M. J. & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

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COMMENTARIES

Intrauterine rhythm and blues?

The continued use of the soporific lullaby over the ages attests to the concept that neonates respond to music. Rhythmic rocking is a phenomenon of motherhood that crosses time and continents. But how early does music influence the human infant? To answer this question requires knowledge of the intrauterine acoustic environment and of the fetal capacity to hear.

Rhythm, a fundamental component of music, is shown to be a feature of the uterine environment where cardiovascular and intestinal sounds emerge intermittently above ambient noise (Walker *et al.* 1971; Benzaquen *et al.* 1990). The average sound level has been measured at 89 dB (linear-weighted), which converts to 65 dB on the A-weighted scale, corresponding more accurately with human hearing abilities (Querleu *et al.* 1981). But is a Beethoven symphony audible in the uterus? External sounds such as the maternal voice, external female and male voices, white noise and pure tones are known to penetrate the uterus with attenuation varying as a function of frequency (Walker *et al.* 1971; Querleu *et al.* 1981). An excerpt from the Bach Brandenburg Concerto No. 1 BWV 1046, presented at 80 dB (linear weighted), was shown to emerge above intrauterine sounds in a study of 8 subjects (Woodward *et al.* 1992). Interestingly, the character of the music was not significantly altered. The greater attenuation of higher frequencies which occurs when sound is transmitted into the body affected the crispness of the attack (articulation) of each note, creating a slightly muffled effect. The rhythms, the textures and the timbres of the various instruments, and the balance of the high, middle and low pitches were not noticeably affected. At certain stages of some recordings, the cardiovascular sounds were particularly loud (probably due to the proximity of the hydrophone to arteries), masking the lower frequencies of the musical instruments during the systolic sounds. Maternal and external female and male singing voices, presented at the normal conversational level of 60 dB, penetrated the uterus. While consonants were indistinguishable, vowel sounds, rhythms, melodic pitch and timbre/character of voices were not noticeably affected. The recordings of the male singing voices (usually provided by an obstetrician) suggest that most obstetricians should stick to their own profession!

Exposing the fetus to Bach may be pointless, however, if the fetus does not have sufficient structural and neurological maturity to perceive sound. Functional maturity of the fetal auditory system is indicated by the structural maturity of the human ear attained by the 24th week of gestation, the activity of the eighth cranial nerve at this stage, and the detection of cortical potentials and auditory brain stem potentials in the preterm neonate of 25 weeks (Anson & Donaldson 1973; Gerber 1977; Starr *et al.* 1977). However, in assessing fetal hearing, one must take into consideration the fluid environment through which the sound is transmitted, the fluid in the middle and external ears, and the transmission of sound by means of bone conduction, the ossicles and the middle ear fluid (Arulkumaran *et al.* 1992).

Response of the third trimester fetus to pure tone or high-pass filtered acoustic stimuli has been well documented (Johansson *et al.* 1964; Grimwade *et al.* 1971; Jensen & Flottorp 1982). These responses are shown to be independent of maternal response, with the occurrence and magnitude of response related to stimulus intensity, frequency, behavioural state and length of gestation (Murphy & Smyth 1962; Dwornicka *et al.* 1964; Tanaka & Arayama 1969; Gelman *et al.* 1982; Jensen 1984; Schmidt *et al.* 1985; Lecanuet *et al.* 1986; Kisilevsky *et al.* 1989). The neonate processes pure tones within the same intensity range as the adult, discriminates location of sound, and is sensitive to differences in frequency, intensity, stimulus rate, the phonetic components of speech and voices (Muir and Field 1979; De Casper and Prescott 1984; Bertoncini *et al.* 1987; Millot *et al.* 1987; Anday *et al.* 1988; Weir and Lamb 1990). The use of fetal and neonatal acoustic capacities for diagnostic and intervention purposes has become common practice (Simmons and Russ 1974; Read and Miller 1977; Trudinger and Boylan 1980; Serafini *et al.* 1984; Duara *et al.* 1985; Marin *et al.* 1987).

Does the fetus respond to music? Little research data is available on the subject (Zimmer *et al.* 1982; Olds 1985; Burns *et al.* 1990). One study determined response to an excerpt from the Bach Organ Prelude BWV 548 in 35 of 40 normal fetuses, from 32 weeks gestational age. Response criteria included a change in fetal heart rate (FHR) of at least 15 beats per minute, occurring within 15 seconds of the stimulus and lasting at least 15 seconds. All non-responses occurred in a period of low FHR variability (Woodward *et al.* 1990).

The perception of sound as noise or music, pleasant or noxious, soothing or alerting, may be a product of learning and conditioning. How the fetus cognitively or psychologically perceives music is a matter of speculation. Considering the discriminatory auditory ability of the neonate, one wonders to what extent the fetus is able to process acoustic information, and to possess auditory memory and learning capacities. Music exists in the passage of time. If the fetus were able to perceive music as more than a series of momentary musical sounds, unrelated to any other, then some degree of auditory discrimination and memory would be required. Investigations of acoustic short-term memory and learning in the third trimester fetus and neonate have shown evidence of habituation with the gradual cessation of response to a repeated acoustic stimulus, conditioning with a new response recruited to a previously neutral stimulus, and operant learning involving modification of behaviour by means of negative or positive acoustic reinforcement (Aldrich 1928; Marquis 1931; Spelt 1948; Bartoshuk 1962; Lipsitt & Kaye 1964; De Casper & Fifer 1980; De Casper & Sigafoos 1983; Brody *et al.* 1984; Lecanuet *et al.* 1986; Shalev *et al.* 1989). Other tests have indicated auditory long-term memory from the prenatal stage, for example, of the maternal voice, maternal heartbeat, uterine sounds, the parental vocal language, and sounds which had been repeatedly presented towards the end of the pregnancy, such as a noise, a passage of spoken prose and the theme tune of a popular television soap opera (Salk 1962; Murooka *et al.* 1976; Rosner & Doherty 1979; Spence & De Casper 1982; Querleu *et al.* 1984; Damstra-Wijmenga 1988; Hepper 1988; Mehler *et al.* 1988).

These studies of auditory response, discrimination, memory and learning provide some indication that the human infant may perceive music, or aspects of it, from the third trimester of intrauterine life. If neonatal behavioural response to familiar music can be verified scientifically, its use may provide welcome relief to parents of otherwise unpacifiable crying babies. Through the process of imitation of the language environment, infants acquire language skill, and toddlers utter their first words after hearing them repeatedly. Music learning, in a similar manner, is influenced by the quality, quantity and context of musical exposure which takes place during and prior to the age at which imitation begins (Suzuki 1969). In the quest to provide an optimal acoustic environment for the young infant, further investigation may provide the necessary clarification regarding the hearing and auditory perceptual and cognitive abilities of the fetus and neonate, indicating the stage at which the human is first influenced by music.

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Antibiotic prophylaxis and caesarean section

Although more than 10 000 women have been enrolled in controlled studies of antibiotics for the prevention of infection following caesarean section, there remains ambivalence over the efficacy. Should prophylactic antibiotics be routinely given to all women, should women undergoing an elective caesarean section receive prophylaxis, what antibiotic is appropriate, when and how should it be given, and for how long? The risk of infection after both emergency and elective caesarean section appears to be substantial. The varying outcomes such as fever, endometritis and wound infection make it difficult to estimate this risk accurately; however, one in four women in the control groups of the randomised studies developed a fever or endometritis.

The increased risk of infection associated with prolonged rupture of the membrane and length of labour is well recognised. Many obstetricians will still not acknowledge the real likelihood of infection after elective caesarean section. Although serious infectious complications are uncommon in this population, data from untreated control groups suggest that one in ten women undergoing elective caesarean section will develop a wound infection and that the incidence of fever or endometritis post-partum is similar to that in the group undergoing emergency caesarean section.

Post-operative infection can certainly be reduced by the use of prophylactic antibiotics. In an overview of 69 controlled studies of antibiotics given at the time of caesarean section, there was unequivocal evidence that the use of antibiotics resulted in both clinically and statistically significant reductions in the incidence of fever or endometritis (odds ratio 0·30, CI 0·27–0·34), wound infection (odds ratio 0·38; CI 0·31–0·45) and serious infection, e.g. pelvic abscess, peritonitis or septicemia (odds ratio 0·24; CI 0·19–0·30).

Evidence from 17 trials of antibiotic prophylaxis for elective caesarean section confirms that prophylaxis also will reduce the risk of febrile morbidity or endometritis (odds ratio 0·30; CI 0·21–0·42) and wound infections (odds ratio 0·45; CI 0·23–0·88). As the rates of infection associated with elective caesarean section are lower than those of an emergency procedure there were too few serious effects in the elective section group to be able to demonstrate a beneficial effect (odds ratio 0·09; CI 0 01–1 57).

Given that there is convincing evidence that antibiotic prophylaxis is indicated for all types of caesarean section, what is an appropriate antibiotic regimen? Infections are generally either wound infections, where *Staphylococcus aureus* is usual, or associated with endometritis, where gram negative aerobes and anaerobes are most commonly implicated. It is reasonable to suppose that an antibiotic regimen chosen for prophylaxis should have activity against at least some of the potential pathogens, but there is no evidence that it needs to be active against all pathogens.

Studies have been published using practically every antibiotic known and all are superior to placebo in reducing infection. Antibiotics with no staphylococcal activity, e.g. metronidazole, and agents with poor activity against resistant anaerobes, e.g. cefazolin, are effective. There is no strong evidence that antibiotics with a broader spectrum of activity such as a second or third generation cephalosporin, are any more efficacious. In the ten trials comparing the three generations of cephalosporins a trend towards an improved outcome with a second or third generation cephalosporin (odds ratio for fever or endometritis 0·82; CI 0·67–1·02) was observed but the difference was not statistically significant. Until further large controlled studies convincingly show that agents with a broad spectrum of activity are better, I currently recommend the use of cefazolin as the prophylactic agent of choice. In the absence of clinical evidence of infection prior to surgery, there is no reason to choose antibiotics such as cefoxitin, cefotetan, cefotaxime or pipericillin for prophylaxis.

It is relatively easy to perform studies of prophylactic antibiotics in caesarean section, as evidenced by the vast number of published trials. The intervention is short and relatively straight-forward and infectious outcomes that are easy to measure occur often. Pharmaceutical companies are eager to include surgical prophylaxis in the approved indications for their drug and support these studies. I am concerned, however, that many of the recent studies performed lack a scientifically valid question. Comparison groups often are inappropriate, costs are not considered and as the new drug is always shown to be as effective or better (because anything works!) implicit approval of the new agent is given. The current preference for studying drugs that have very broad antimicrobial activity as prophylactic agents must not be condoned.

Recent trends in surgical antimicrobial prophylaxis are for shorter courses to be given, with one or at the most two doses. There have been 17 studies that have examined the question of length of prophylaxis in caesarean section; no statistically significant difference between one dose and 3–5 doses of antibiotic on fever or endometritis has been demonstrated (odds ratio 1·09; CI 0·86–1·39). In an overview of five trials that compared a one day course of antibiotics with a 3–5 day course, the longer course may have been more effective in preventing post-partum infection (odds ratio for fever or endometritis 1 80; CI 1·11–2·93). Subclinical infection already present at the time of caesarean section could explainthe failure of a short prophylactic course. Further clinical trials may be useful, however, to identify those patients in whom longer treatment is warranted

Antibiotic irrigation or peritoneal lavage at the time of caesarean section will prevent post-partum infection and eight controlled trials have clearly shown a reduction in fever or endometritis (odds ratio 0·24; CI 0·18–0·31) and serious infections (odds ratio 0·27; CI 0·16–0·46). When peritoneal irrigation is compared to systemic antibiotics, there is no significant difference between the groups although a trend approaching statistical significance for an increase in wound infections with antibiotic irrigation was observed (odds ratio 2·96; CI 0·99–8·91).

Unfortunately, despite the thousands of women who have been involved in trials of prophylaxis, information on adverse events following prophylactic antibiotics is scanty and generally poorly collected. Although there is an acknowledged reluctance to give any drugs in pregnancy, all antibiotics, apart from tetracycline, are likely safe for the mother and infant if appropriately administered. It has become a routine practice to try to prevent exposure of the baby to any antibiotic by giving the first dose to the mother after the cord has been clamped; while not unreasonable it probably is being over-cautious given the safety of the drugs used for prophylaxis. There is, however, the theoretical concern that prophylactic antibiotics may decrease the chance of culturing an infecting organism and this may be a valid argument for waiting until the cord is clamped, albeit at the expense of possibly decreased effectiveness of prophylaxis. Principles of surgical prophylaxis have established that the maximum concentration of antibiotic should be present in the tissues when the incision is made.

An argument against routine antibiotic prophylaxis is concern about the potential development of resistant organisms. This is a real issue but unfortunately the magnitude of the problem is unknown because few studies have prospectively looked for resistance. Shortening the duration of prophylaxis and avoiding the use of broad spectrum agents should minimize the development of resistant bacteria. The microbiology laboratory should regularly monitor the antibiotic sensitivity pattern of clinical isolates to detect changes.

The evidence strongly supports the routine use of prophylactic antibiotics for caesarean section. No particular regimen is clearly superior; cefazolin is cheap and effective and, unless there are other contributing factors, should be the standard regimen. Unless infection is already present, two or at the most three doses of antibiotic are adequate and systemic treatment is preferable to local peritoneal irrigation. There is no good evidence that side effects are so significant that they outweigh the benefits of prophylaxis. The administration of prophylactic antibiotics should be standard care for patients undergoing caesarean section.

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OBSTETRICS

Antenatal cardiotocogram quality and interpretation using computers

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ABSTRACT

Objective To test the application in practice of computerized fetal heart rate (FHR) analysis in pregnancy.

Design Randomized distribution of subjects with computerized analysis automatically revealed or concealed.

Setting A district general hospital and a teaching hospital outside London.

Subjects 2869 pregnant women studied within a year.

Outcome measures Quality and duration of the cardiotocogram; quantitative measurement of FHR variation; number of stillbirths.

Results With interactive advice to the operator, records were of improved quality (up to 28% without signal loss) with potentially much reduced recording time. The short-term FHR variation measured in the last records before intervention is reported for the first time.

Conclusion The benefits of using the computers include improvement in record quality and saving of time. In addition, where interpretation depended on estimation of FHR variation there was prima facie evidence of observer misinterpretation; visual analysis was unreliable. A larger trial is now required with more rigorous constraints on intervention.

Computerized analysis of the fetal heart rate (FHR) antenatally provides advantages over visual analysis (Dawes *et al.* 1991*a*). These include better quality records, better use of time spent recording and adjustment for changing fetal behavioural states. We describe the results of a study undertaken to test its application in practice, using a randomized distribution of subjects to measure the change in record quality.

The results of the numerical analyses were presented in relation to normal ranges; warnings about extreme values were given but standardized responses to different patterns were not mandatory The planned size of the study was small and not expected to permit conclusions about whether computerized analysis conferred clinical benefit. Nevertheless, there was evidence that subjective misinterpretation could be avoided by computerized measurement.

Subjects and methods

Randomization

Over a period of 1 year, antenatal FHR records were recorded and analysed using APRICOT XEN computers interfaced to HP8040A fetal monitors in the Luton and Dunstable District General Hospital (3333 records, 1579 patients) and in the Princess Anne Hospital, Southampton (3197 records; 1285 patients). These comprised 29% of all women delivered annually in both hospitals, and who were considered to be at high risk.

Based on a calculation from the hospital number (entered with the woman's name on the computer at the start of each record) the computerized records were either revealed on the computer monitor and printed or concealed. In either case the data were filed and, though inaccessible to the operator when concealed, were all subsequently analyzed. Cardiotocograms were always available. Since the hospital number was specific to each woman, all her records were either revealed or concealed. When the record was concealed, the computer displayed the patient's name and hospital number, 'Recording' and a dot added every 1/16th minute.

Fetal heart rate analysis

The system of computerized analysis has been described previously (Dawes *et al.* 1985). Valid fetal pulse intervals (Dalton *et al.* 1977) were averaged over 1/16 min and a baseline was fitted (Dawes *et al* 1982*a*). Signal loss was defined as the proportion of 1/16 min epochs for which no valid FHR values were available. Failure to stop recording before detaching the transducers from the woman's abdomen sometimes resulted

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in apparent signal loss at the end of a record; such artefacts were removed before the final analysis.

Variations in rate around the baseline FHR were detected as accelerations (>10 beats/min and >15 s) or decelerations (>10 beats/min and >1 min, or >20 beats/min and >30 s). Large decelerations were defined as having an area (below the baseline) >20 lost beats. Erroneous or doubtful decelerations and accelerations were identified (Dawes *et al.* 1990*a*) and excluded.

Long-term FHR variation was defined as the mean minute range of pulse intervals about the baseline, and short-term ($^1/_{16}$ min epochal) variation as the mean epoch-to-epoch variation, averaged over the record, and expressed in milliseconds (ms). The calculations are illustrated and the linear relation between short and long-term variation is described in more detail elsewhere (Dawes *et al.* 1990*b*; Street *et al.* 1991). In calculating FHR variation decelerations were excluded. Episodes of high or low FHR variation were identified as 5 of 6 consecutive minutes in each of which the range of pulse interval was >32 ms or <30 ms respectively (Dawes *et al.* 1985). Basal FHR was measured in episodes of low variation, where present, and otherwise from the modal or 'peak' value (Dawes *et al.* 1982*a*) to avoid bias through prolonged accelerations. Episodes of high long-term FHR variation are preferred to accelerations as evidence of normality for reasons already described (Dawes *et al.* 1982*b*).

In revealed records, advice was given to stop recording if, after 10 min, an episode of high FHR variation had been detected and no abnormality (e.g., FHR deceleration or basal rate >160 beats/min) was present. Otherwise the computer advised that recording be continued until these conditions were satisfied (analyses were repeated every 2 min thereafter), or until 60 min. At any time, if signal loss exceeded 30% in 5 min, audible and flashing visual signals were generated to advise adjustment of the ultrasound transducer. Results were printed as illustrated elsewhere (Dawes *et al.* 1985) and in addition warnings were printed when records were preterminal (short-term variation <3 ms). or likely to be sinusoidal (Dawes *et al.* 1990*b*). Table 1 shows the normal values, lower limit of normality and the values derived for preterminal and terminal classifications based on outcome (Street *et al.* 1991; Dawes 1991) in a database of more than 20 000 records. In that analysis the incidence of fetal acidaemia (umbilical artery base deficit >12 mM and pH <7·12) or intrauterine death was 38% when short-term variation <2·6 ms, and 9% when 2·6–3 ms. In the present study, these classifications were offered as advice, and were not mandatory in the determination of treatment. Ethical approval was given by the appropriate local committees. The different statistical analyses are noted in the text.

Table 1. Limits of normality in short- or long-term fetal heart rate (FHR) variation at 32 weeks gestation.

FHR variation (ms)	Short-term	Long-term
Normal	8·1 (0·3)	44·4 (1·5)
Lower limit of normality (3%)	5·7 (0·3)	31·4 (1·5)
Chronic hypoxaemia	3·7 (0·2)	20·6 (1·2)
Preterminal*	≤3·0	[<16·5]†
Terminal*	≤2·6	—

*Based on 99 patients: at this low level of FHR variation short-term variation is preferred because it eliminates the confounding effect of slow sinusoidal oscillations (Street *et al.* 1991).

†Calculated from the overall linear relation between short and long-term FHR variation.

Results

Randomization

Figure 1 shows the number of records collected by the computerized systems (2 each in Southampton and Luton) divided by gestational age in 2 week periods and concealed or revealed at the bedside. There were approximately equal numbers concealed (3182 records from 1413 patients) or revealed (3350 from 1451 patients). The modal gestational age in those concealed was 37 weeks (401 records); in those revealed it was 36 weeks (419 records).

Record quality

When the computerized record was revealed, current calculated signal loss was displayed continuously. When signal loss was high, audible and visible warnings were given to adjust the transducer. In Southampton the midwives were encouraged to pay attention to such interactive commands generated by the computers when records were revealed. In Luton policy was not defined in this respect. Consequently the results were different in the two units.

Table 2 shows the proportion of records of good quality (zero signal loss) or otherwise in the two hospitals, from 27 to 42 weeks, and whether concealed or revealed. When results were concealed the distribution of records by signal loss was very similar in the two hospitals. In Southampton, a comparison between revealed and concealed showed an increase in

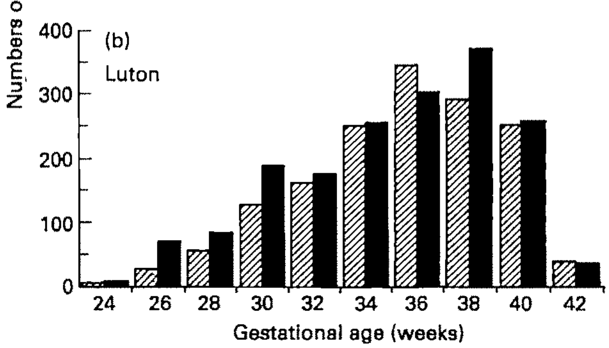

Fig. 1. Distribution of numbers of records, revealed or concealed, by gestational age. (a) Southampton ▨ concealed· 1595; ■ revealed: 1602. (b) Luton ▨ concealed: 1587; ■ revealed. 1748.

Table 2. Proportion of records with signal loss of differing size, concealed or revealed and by hospital, at 27–42 weeks gestation

	Hospital			
	Southampton		Luton	
Signal loss %	Concealed (*n* = 1595) (%)	Revealed (*n* = 1587) (%)	Concealed (*n* = 1564) (%)	Revealed (*n* = 1711) (%)
0	2·0	27·8	2·3	17·5
0·1–2	24·5	28·9	22 6	26·4
2–4	25·6	13 3	25·0	16·0
4–6	15·2	7 6	15·5	10·3
6–8	7·1	4 9	8·9	7·5
8–10	5·6	3·5	5·9	4 6
10–20	12·3	10·0	13·5	12·2
>20	7·7	4·0	6 3	5·5
Total	100	100	100	100

the proportion of records with no signal loss from 2% to 27·8%, and a decrease from 7·7% to 4·0% in those with signal loss more than 20%. In Luton the improvement in revealed records also was present, but smaller. The difference between the distributions of signal loss, in revealed as compared with concealed records, was highly significant ($P<0{\cdot}001$) in both hospitals (Kolmogorov-Smirnov non-parametric test, Siegel & Castellan 1988). We concluded that the use of computerized analysis on-line ensures better quality records, but that to achieve the best results the midwives must be encouraged to pay attention to interactive advice from the computer.

The midwife normally acquires a good signal before recording, often in episodes of low FHR variation; thereafter fetal and maternal movements cause deterioration. For example, in 1322 concealed records lasting 30 min or more, 39% had no signal loss before 15 min, but only 22% had no signal loss by 30 min. Thus shorter records tend to be of better quality. What is of more practical concern is that over the first 5 min, 7·3% of these records had signal loss ≥20%; over the next 5 min there was no improvement, 8·3% had signal loss ≥20% (range 20–100%; median 35%, mean 39%). It is within this group that readjusting the ultrasound transducer, or restarting the record, can reduce the incidence of useless records.

Many records with high signal loss are difficult to interpret.

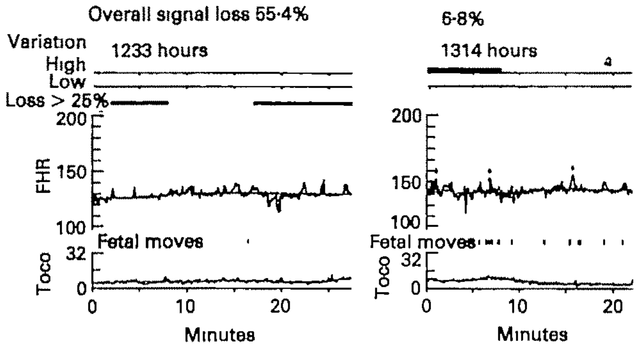

Fig. 2. A record at 30 weeks gestation with high signal loss (55·4%) which, on repetition at once, had better quality (6·8% signal loss). Both records were concealed. The dots show the fitted baseline

In both hospitals together there were 63 (1%) records with signal loss in excess of 40% (37 concealed, 26 revealed), most of which (87%) could not be interpreted through lack of episodes of high FHR variation or otherwise. There was no relation with gestational age (27–42 weeks). On only ten occasions were the records repeated the same day; in nine, the quality of the second record was much better than that of the first (e.g., Fig. 2). In 23 of the 63, poor quality records the duration was less than 15 min (concealed in 13, revealed in 10), but only five were repeated the same day. It therefore seems unlikely that the option of a further record (considered) was abandoned from lack of time. Since analysis was retrospective we cannot tell whether vigorous activity was sometimes accepted as sufficient reassurance of fetal health when record quality was poor.

Record duration

The policy (not always followed, e.g., with high signal loss) was to record FHR traces for at least 20 mins, more if the record was not recognized as normal by visual criteria. In Southampton the mean duration of records was 29·6 (SE 0·3) min (concealed) or 24·2 (SE 0·3; revealed); in Luton the corresponding figures were 30·8 (SE 0·3 min) (concealed) or 27·5 (SE 0·3) (revealed). However, record duration depends to some extent on gestational age. Table 3 shows the duration of records for patients where revealed, and the time advised by the computers; at all ages the mean record duration was greater than advised.

Figure 3 shows the proportion of records of different durations (10, 11–14, 54–57, 58–59 and 60 min) according to whether they were concealed or revealed, and where advice was given by the computer to stop recording. There are several points. First, of the records where advice was given to stop recording, 53·7% were reached in 10 min. Secondly there was a minor peak in the same group (solid column) at 19–22 min, approximating to the mean duration of state 1F (fetal quiet sleep) near term (van Vliet *et al.* 1985); thereafter the proportion of such records fell rapidly. Thirdly, at 60 min the proportion of concealed records (6·0%) was greater than those revealed (4 4%), and both were greater than those in which the computers still advised continuation of recording (1·0%) and which were thereafter questionable or abnormal. And fourthly, many records were interrupted before 20 min, whether revealed or concealed, sometimes perhaps because of great fetal movement.

Table 3. Duration of records (minutes) where computerized advice was revealed at the bedside, compared with the times when the computer advice was to stop recording.

	Hospital			
	Southampton		Luton	
Gestational age (weeks)	Actual	Advised	Actual	Advised
26–31	24·1 (0·9)	17 7 (0 6)	31·5 (0 7)	15·7 (0·6)
32–36	24·4 (0·5)	15·5 (0·4)	27 0 (0·4)	14·7 (0·3)
37–40	23·7 (0·5)	15 0 (0 3)	25·1 (0·4)	14·2 (0·3)
41–42	26·5 (1·3)	15·4 (0 8)	22·8 (0 4)	16·4 (0 7)

Data are means (SE) values by gestational age.

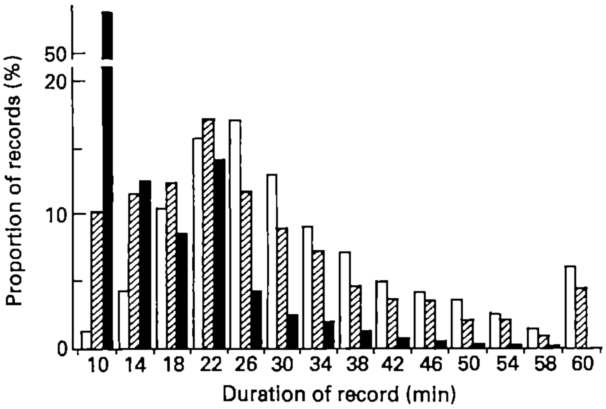

Fig. 3. Distribution of record lengths when concealed or revealed, or when advised to stop recording (both concealed and revealed). □ concealed. 3181; ▨ revealed· 3349; ■ advised: 5917.

In 546 records (8·4% of the total), recording was stopped before 60 min and before the computer had advised stopping. Four hundred (73%) of these records were stopped before 30 min. Table 4 shows the analysis of these data. While 230 of these records contained three or more accelerations (of at least 10 beats/min amplitude and 15 s duration), there were only 22 with gross (>40%) signal loss and 24 possibly attributable to mechanical failure. This leaves 337 (5·2% of all records) unaccounted for, in which there was no adequate reason given for stopping; 55% were concealed records and 45% revealed. It is evident that the advice given by the computer to the nursing staff 'TO CONTINUE' was often ignored, and that this resulted in records which were misleading, because FHR variation was low, and inadequate time was allowed for an episode of high variation to appear.

The mean duration of records advised by the computer was 15·5 min, which agrees with that of an independent series from Oxford (16·1 min). The potential saving in recording time in the two centres over a year is calculated as more than 1600 h.

Records with low long-term FHR variation

An important feature of the computerized analysis is that FHR variables (FHR variation, basal FHR and decelerations) and the incidence of fetal movements are measured. Of these variables, there is strong evidence that FHR variation is the most important (Street *et al.* 1991). We therefore investigated outcome where FHR variation (long-term) was <22 ms based on a previous study (Smith *et al.* 1988).

Table 4. Analysis of records stopped before the computers advised.

	Number of records		
	Revealed	Concealed	Total
Record stopped without advice	342	271	613
Records with 3 or more accelerations	126	104	230
>50% signal loss	15	7	22
Possible mechanical failure*	15	9	24
		Total	276
Unaccounted			337

*E.g. mains disconnection, or 'reset' pressed.

There were 43 records with abnormally low FHR variation, and no episode of high variation, which were short (<40 min), too short to be sure that an episode of high variation (i.e., of active sleep, state 2F) would not have ensued had recording been continued; these records could not be interpreted with certainty. In 12 instances this fact was recognized by the user, who repeated the record at once, sometimes because of high signal loss in addition. Of the remainder there were more concealed (21) than revealed (10); this was unrelated to gestational age (28–42 weeks). The mean record duration was not significantly different whether concealed (24·4 SE 1·5 min) or revealed (23·9 SE 2·8 min), nor was the mean long-term FHR variation different during low FHR variation (concealed 14·8 SE 0·7 ms; revealed 14·7 SE 0·6 ms). Of the 31 women from whom these records were made, five were subsequently delivered by caesarean section for fetal reasons at 29–32 weeks gestation, within the next 10 days and in the absence of labour.

There were 41 women (1·4%) with, at any time, long-term FHR variation <22 ms, verified by records of 50–60 min. Excluding those delivered for maternal reasons or by spontaneous preterm labour, 26 were delivered by caesarean section for fetal reasons in the absence of labour. Short-term FHR variation in the last record before delivery was not significantly different with gestational age, before (3·5 SE 0·4 ms) or after 32 weeks (3·3 SE 0·2 ms), nor whether revealed or concealed. Figure 4 shows the data. Of the 11 fetuses born by caesarean section before 31 weeks gestation, six had short-term FHR variation well above (3·4–5·0 ms) the preterminal value (3·0 ms, Table 1).

In the remaining 13 women, labour was induced at 35–40 weeks gestation at a mean short-term FHR variation of 4·1 (SE 0·3) ms. There was no significant difference in variation from those managed by caesarean section (Mann–Whitney *U* test). In all but two of these women the records were concealed. The incidence of operative delivery for fetal distress in labour was high (6 of 13 = 46%, all but one by caesarean section).

It was agreed that there should be no mandatory action, so

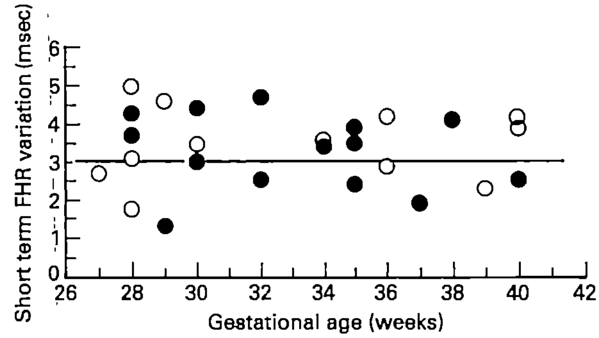

Fig. 4. Short-term FHR variation in the last records of women delivered by caesarean section for fetal reasons, by gestational age and according to whether the records were revealed (○) or concealed (●). The horizontal line is drawn at the value (3 msec) designated preterminal (Table 1).

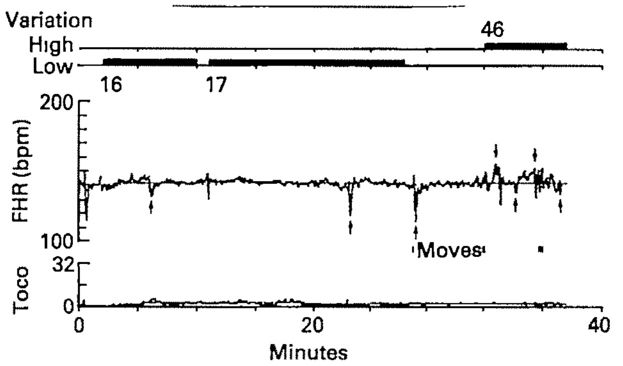

Fig. 5. Revealed record of a woman, at 40 weeks gestation in which an episode of high FHR variation with movements was not identified until more than 40 min. The patient was sectioned at once in spite of this evidence of normality.

we cannot determine whether the revealed analyses influenced clinical action. In retrospect, however, there are causes for concern. Thus two women had sections at 40 weeks gestation for an 'abnormal FHR record', although their revealed records showed a normal episode of high FHR variation (e.g., Fig. 5). Another woman, with the help of the synoptic plot which was concealed (Fig. 6), might have been delivered 24 h earlier when short-term variation fell to 2·3 ms, a terminal value (Street *et al.* 1991). The outcome was a neonatal death at 29 weeks gestation of uncertain diagnosis (severe respiratory distress syndrome, persistent fetal circulation, hypoglycaemia, hypotension, neutropenia and possible viral infection); preterm delivery with metabolic acidaemia is likely to be fatal. Two women at 36 and 41 weeks gestation with very low short-term FHR variation (2·8–2·9 ms, one concealed and one revealed) were induced; in both fetal distress developed in labour, requiring operative delivery (section or forceps). The extra hazard to the fetus might have been anticipated, given the exceptionally low FHR variation.

Stillbirths and neonatal deaths

During the year there were 45 stillbirths. CTG records had been obtained from 10, but in only two were they within a week of death; both were single records taken the day before death at 38–40 weeks gestational age. Both fetuses had a history of reduced movements. One (concealed) had a record, 25 min long with 36% signal loss, and so impossible to analyze satisfactorily. The other (revealed) was only 12 min long, showed no fetal movements, was otherwise normal (long-term variation 71 ms) but was interrupted inappropriately (since there had been no recorded movement) by the user.

We also examined the 47 neonatal deaths to be sure that no other possible correlations between FHR analysis and outcome had been overlooked. One neonatal death has already been considered; there were no others which illuminated the interpretation of FHR analysis before birth.

Discussion

The computers were accepted readily by the nursing staff and the women. Randomization of concealed/revealed records was necessary because quality (% signal loss) varies with gestational age (Dawes *et al.* 1985). The results show that randomization of records and women was satisfactory by gestational age (Fig. 1) and in respect of the distribution of concealed or revealed abnormal records of those sectioned for fetal reasons (Fig. 4). This system of randomization has therefore been adopted for the large multi-centre trial of antenatal computerized analysis organized by the EC Concerted Action Project 'New Methods of Perinatal Surveillance'. The decision by the two hospitals to adopt a conservative approach, recording many records for 20 min or more, had the advantage that we were able to measure quality and analyze interpretation in conditions close to conventional usage.

As with all instruments, the accuracy of fetal monitors should be examined; it was low (Dawes *et al.* 1981). There is a dearth of published studies on the subject. Record quality using ultrasound has been compared (Lawson *et al.* 1982) with or without autocorrelation and with direct ECG recording (Lawson *et al.* 1983). The high mean signal loss observed using a computer interfaced to a fetal pulse ultrasound peak detector (HP 8031: mean about 20%; Dawes *et al.* 1981; 1982b) was reduced by using autocorrelation (HP 8040; Dawes *et al.* 1985). A further improvement was made by programming the computer to detect and eliminate 'outliers', erroneous or dubious decelerations and accelerations (Dawes *et al.* 1990*a*). Different fetal monitors differ in their generation of such outliers (Dawes 1992) The present study shows that there is still room for improvement in reducing the occurrence of records with high signal loss. An improvement can be made by requiring a second record when the first is of poor quality; yet it is evident that simply pointing out the high

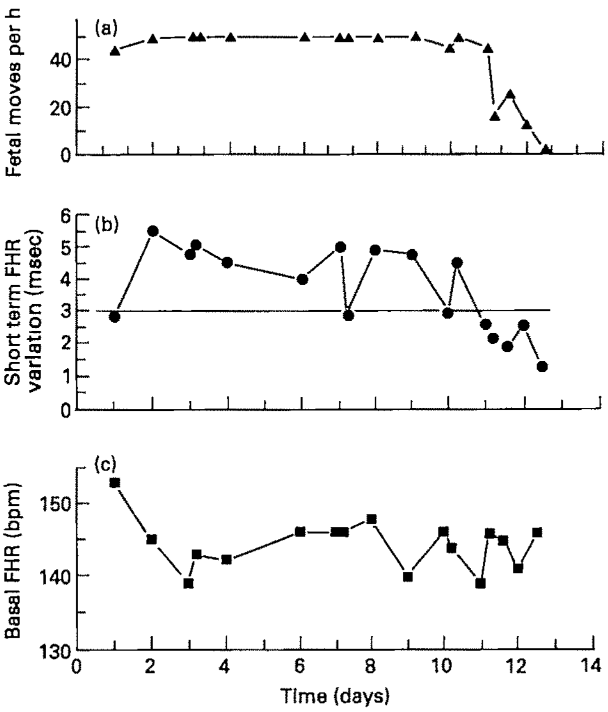

Fig. 6. Synoptic plot of fetal movements (a), short-term FHR variation (b) and basal FHR (c) of a fetus at 29 weeks gestation. The computerized records were concealed.

signal loss on the screen and printed record is insufficient to ensure that a second record is made. As poor quality is often due to transient phenomena, such as vigorous fetal movement or hiccoughs (Dawes *et al.* 1985), it is not surprising that another record made at once can be astonishingly better (Fig. 2). It is a feature of cardiotocograms that, after 28 weeks gestation (Dawes 1982*b*) the accelerations contributing to an episode of high FHR variation are accompanied by clusters of fetal movements which can give rise to signal loss during that episode. They are biased towards lower quality when quality should be best.

Record duration can be decreased when the users interact with computer advice, on records which are revealed. There is an advantage in adjusting the duration of the record by criteria now based on the analysis of more than 20 000 antenatal FHR records over 9 years clinical practice, but this advantage is only achieved when the advice to stop or to continue recording is followed rigorously. Otherwise, as the results show, records will be obtained which cannot be interpreted rationally, e.g., when the record starts with a prolonged episode of low variation, which may last more than 40 min, but is curtailed by the user. It is a matter of concern that the instructions on record taking were often ignored.

An important feature of the computerized system of analysis is that FHR variation is measured. It has been shown repeatedly that visual estimation of FHR variation is unreliable (Trimbos & Keirse 1978; Lotgering *et al.* 1982; Flynn *et al.* 1982; Borgotta *et al.* 1988). The practical effects concern several aspects of FHR variation. Firstly, when FHR variation is already low, it is difficult without measurement to estimate whether the variation is decreasing day by day. This problem is illustrated in Fig. 6 (computerized analysis concealed) where no intervention was made for 30 h after a very flat record with reduced movements. Secondly, before 32 weeks gestation and without measurement it is difficult to be sure that FHR variation has reached a preterminal or terminal value, when preterm delivery is necesssary to avoid acidaemia or intrauterine death. Thus in Fig. 4 there is a wide range of values for short-term FHR variation in the last record before caesarean section. Measurement permits a better determination of the time when action becomes necessary. Thirdly, there is the problem of interpreting visually a record with a long episode of low FHR variation, succeeded after 40 min or more by an episode of high FHR variation, which often initially is not of great amplitude. Such cyclic changes in the amplitude of FHR variation persist in labour, also without a sinister connotation (Dawes *et al.* 1991*b*). In the instance shown (Fig. 5) the record was revealed and attention was drawn to the episode of high variation, accompanied by fetal movements, on the printed output. Nevertheless, treatment was not conservative; the woman had a section.

There are two criticisms to be made. First the number of fetuses with preterminal low heart rate variation (<3 ms short-term) was only 12 (6 at <32 weeks gestation); we had expected more than twice as many, based on experience in Oxford and taking into account the numbers of deliveries annually. A larger trial is required, and this is now underway in Europe. Secondly, it is evident that fuller instructions should be given to use the computerized system as it was designed to be used, (i.e., by following interactive commands to ensure the best use). Better interpretation of revealed records could have been made, perhaps by mandatory guidance. Interpretation is often difficult, because of the many factors which may determine the decision to intervene in high risk pregnancies, maternal as well as fetal. The computer is no substitute for judgement, but provides objective data on which this can be based.

There were 45 stillbirths in the year. In only two of these pregnancies had a recent FHR record been taken, with a history of reduced fetal movements. In some instances stillbirth was associated with abruption. In others there was no clear evidence of the cause of death. To detect and understand the nature of stillbirths in the last trimester requires another strategy, e.g. such as a more detailed surveillance of the fetus when reduced movements are reported.

Acknowledgment

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OBSTETRICS

Evidence against a pathogenetic role for endothelin in pre-eclampsia

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ABSTRACT

Objective To assess whether increased placental or systemic endothelin synthesis has a pathogenic role in pre-eclampsia (gestational proteinuric hypertension).

Design Prospective observations study.

Subjects 19 women with pre-eclampsia and 10 healthy pregnant women were studied. All were in the last trimester.

Main outcome measures Preproendothelin-1 gene expression by Northern blot analysis and generation of endothelin-1 precursor, big-endothelin-1, and endothelin isoforms, namely endothelin-1, 2 and 3, were assessed by specific radioimmunoassays, in placental tissue. Plasma endothelin-1 levels and urinary excretion of big-endothelin-1 and endothelin-1 were measured.

Results Placental preproendothelin-1 gene expression and immunoreactive big-endothelin-1 and endothelin-1, 2 and 3, were comparable in placental tissue from pre-eclamptic and normal pregnant women. Plasma levels of endothelin-1 did not differ between pre-eclamptic and normal pregnancies. In contrast, urinary excretion of endothelin-1, which is likely to reflect the renal synthesis of the peptide, was significantly decreased in pre-eclamptic, as compared with normal pregnant women. This was not due to a decreased renal generation of endothelin-1 precursor, since urinary excretion of big-endothelin-1 did not differ between pre-eclamptic and normal pregnancies. These data suggest an increased renal endothelin-1 breakdown in pre-eclampsia.

Conclusions Endothelin is unlikely to play a role in the pathogenesis of pre-eclampsia. Instead, an increased renal breakdown may have a role in limiting the negative effects of other vasoactive factors on the renal circulation.

Pre-eclampsia, a syndrome of hypertension and proteinuria, develops in 5% of first pregnancies and in 1% of multigravid women (Davey & MacGillivray 1988) and is the most common cause of maternal and fetal morbidity and mortality (Lindheimer *et al.* 1987). The cause of pre-eclampsia is still undefined. Unlike normal pregnant women, who are refractory to the pressor effect of angiotensin II, pre-eclamptic women lose such refractoriness as early as 18–22 weeks' gestation (Gant *et al.* 1973). Among the several possible explanations for such abnormality is an increased biosynthesis of thromboxane A2, a potent vasoconstrictor (Ellis *et al.* 1976), which is elevated in pre-eclampsia (Fitzgerald *et al.* 1990), without a parallel increase of prostacyclin (Fitzgerald *et al.* 1987).

The discovery that endothelial cells in culture generate endothelin-1, a potent vasoconstrictor (Yanagisawa *et al.* 1988), opened new perspectives into the endogenous control of vascular tone. Infusion of endothelin-1 induces a long-lasting elevation of systemic blood pressure in anaesthetised dogs and rats (Inoue *et al.* 1989; Miller *et al.* 1989) by virtue of its vasoconstrictor activity that increases peripheral vascular resistances.

We have reported previously (Benigni *et al.* 1991a) that placental tissue from normal pregnant women expressed preproendothelin-1 gene and generated different isoforms of endothelin, namely endothelin-1 (as well as its precursor big-endothelin-1), endothelin-2 and endothelin-3. Very recently others (Kamoi *et al.* 1990; Taylor *et al.* 1990; Nova *et al.* 1991) have found changes in systemic levels of endothelin in pre-eclampsia and suggested that an excessive endothelin synthesis may play a pathogenetic role in pregnancy-induced hypertension. The aim of the present study was to prove or disprove such a hypothesis.

Subjects and methods

The study group consisted of 19 women admitted for moderate to severe pre-eclampsia to the Obstetric Divisions of the Ospedali Riuniti di Bergamo and of the Spedali Civili di Brescia. All had blood pressure values above 140/90 mmHg, recorded on two occasions at least 6 h apart, and significant proteinuria (>0·3 g/24 h) (Davey & MacGillivray 1988). Two pregnancies were complicated by the HELLP syndrome.

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Antihypertensive treatment included the calcium antagonist, α-methyldopa, and magnesium sulphate. All the women were delivered by caesarean section within 48 h of admission. One had a twin pregnancy. Ten of the infants were small for gestational age according to the distribution of normal weights for gestational age reported by Bossi *et al.* (1980).

A comparison group of 10 normotensive pregnant women admitted for delivery was also studied. All the women in the comparison group were of similar age and parity to the hypertensive group (range 22–40 years). Their blood pressure was normal on admission and they had no significant proteinuria. None had taken any drugs. One woman had a twin pregnancy and was delivered after the spontaneous onset of the labour at 32 weeks' gestation. All ten were delivered within 48 h of admission to the hospital.

Pre-eclamptic and normal pregnant women were studied on admission to the hospital after first giving their informed consent. The characteristics of all the women and their babies are reported in Table 1.

Placentas from five pre-eclamptic and five normotensive pregnant women were processed within 30 min of collection. The clinical data for these subgroups of women are reported in Table 2. Total RNA from placental fragments (2–3 g) was prepared by guanidium isothiocyanate extraction and centrifugation through caesium chloride (Rambaldi *et al.* 1987). Poly (A)+ RNA was then selected by oligo(dT)-cellulose column chromatography (Sambrook *et al.* 1989). Placental mRNA (10 µg) and total RNA from human umbilical cord endothelial cells (HUCEC) (10 µg) were then fractionated on 1·2% formaldehyde agarose gel and blotted onto synthetic membranes (Gene Screen Plus, New England Nuclear, Boston, MA). A human preproendothelin-1 probe was labelled to a specific activity of 109 cpm/µg by using hexanucleotide primers and (α-^{32}P)dCTP (Feinberg *et al.* 1983). Membranes were hybridised with ^{32}P-labelled preproendothelin-1 cDNA (Zoja *et al.* 1991) and with mouse α-actin cDNA (Minty *et al.* 1981), taken as internal standard for total RNA content, and exposed to X-ray film for autoradiography.

Big-endothelin-1, endothelin-1, endothelin-2 and endothelin-3 concentrations from the placentas were assessed after extraction and HPLC purification of the tissue (1–2 g), as described previously (Benigni *et al.* 1991a). The content of big-endothelin-1, endothelin-1, endothelin-2 and endothelin-3 was measured by radioimmunoassay (RIA) in HPLC fractions co-eluting with the corresponding authentic standards. Protein content of placental tissue was determined by the method of Lowry *et al.* (1951).

For plasma endothelin-1 level measurements, blood was collected with EDTA (2 mg/ml) and aprotinin (500 kallikrein inhibitor U/ml) on admission to the hospital. Plasma samples (5 ml) were extracted on Sep-Pak C18 cartridge as described for placental tissue and lyophilised until assayed.

An aliquot (5 ml) of overnight urine samples collected over 6–8 h at admission to the hospital was run on a Sep-Pak C18 cartridge, eluted with 85% methanol and lyophilised until assayed. The extraction recovery for all the peptides measured averaged 80–85% for placental tissue, 65–75% for plasma and 70–85% for urine.

Extracted samples were resuspended in phosphate buffer (pH 7·2) and big-endothelin-1, endothelin-1, 2 and 3 content was determined by specific radioimmunoassay as described (Benigni *et al.* 1991a). The detection limits of the assays were 0.4 pg/tube for endothelin-1, 2 pg/tube for endothelin-2 and endothelin-3, 3·1 pg /tube for big-endothelin-1. Endothelin-1 and 2 were measured by an anti-endothelin-1 antibody largely cross-reacting with endothelin-2 (46·9%). Cross-reactivity of anti-endothelin-3 antibody was: endothelin-1: <2%, endothelin-2: <1% Cross-reactivity of anti-big-endothelin-1 antibody against endothelin-1, 2 and 3 was <1·8%. Intra-and inter-assay variability averaged 9% and 14%. Urine creatinine was measured by alkaline picrate method (Bonsnes & Taussky 1945).

All results are expressed as mean (SD) and median values. Data were analysed by the Mann Whitney *U* test. The significance level was taken to be <0·05. The 95% confidence intervals for the difference between median values were used for plasma endothelin-1 levels.

Table 1. Characteristics of pre-eclamptic and normal pregnant women.

Variable	Pre-eclampsia (*n* = 19) mean (SD) (range)	Normal pregnancy (*n* = 10) mean (SD) (range)
Age (years)	31·1 (4·1) (25–38)	29·3 (6·1) (22–40)
Nulliparous	13	7
Multiparous	6	3
Gestational age at the time of investigation (weeks)	32·6 (2·7) (29–38)	38·3 (3·4) (32–41)
Mean arterial pressure (mmHg)	122·1 (9·2) (108–143)	96·3 (8·1) (86–103)
Proteinuria (g/24 h)	3·5 (2·4) (0·5–8·0)	0
Birthweight (kg)	1·7 (0·57) (1–3)	3·1 (0·52) (2·4–4·0)
Small for gestational age	10	0
Placental weight (g)	369 (142) (190–650)	593 (70·1) (480–700)

Table 2. Characteristics of women whose placentas were analysed for preproendothelin-1 mRNA.

Variable	Pre-eclampsia (*n* = 5) mean (SD) (range)	Normal pregnancy (*n* = 5) mean (SD) (range)
Age (years)	32 (3·7) (28–38)	28·2 (7·2) (22–40)
Nulliparous	4	3
Multiparous	1	2
Gestational age at the time of investigation (weeks)	31·1 (1·5) (29–33)	40·2 (0·4) (37–41)
Mean arterial pressure (mmHg)	123·6 (12·0) (110–143)	100 (5·4) (92–105)
Proteinuria (g/24 h)	3·0 (3·5) (0·5–8·2)	0
Birthweight (kg)	1·4 (0·5) (1·0–1·8)	3·3 (0·4) (2·8–4·0)
Placental weight (g)	316 (57·7) (230–350)	596 (78) (480–700)

Results

Fig. 1 shows a Northern blot demonstrating a single 2·3 kb preproendothelin-1 mRNA expressed in placental tissue from pre-eclamptic and normal pregnant women. As a positive control for preproendothelin-1 gene expression, total RNA isolated from umbilical vein endothelial cell was used. As shown in Fig. 1, a transcript of comparable intensity was found in placental tissue from women affected by pre-eclampsia and normal pregnant subjects. Subsequent quantification of actin mRNA and analysis of the optical density of the autoradiographic signals confirmed that there was no difference in the preproendothelin-1 mRNA levels between pre-eclamptic and normal pregnancy. Fig. 2 reports big-endothelin-1, endothelin-1, endothelin-2 and endothelin-3 concentrations in tissue extract from placenta obtained from pre-eclamptic and normal pregnant women. Consistent with the results of preproendothelin-1 gene expression, the mean concentrations of all the peptides extracted from the placentas of pre-eclamptic women were similar to those measured in placentas from normal pregnancies [big-endothelin-1: 7·3 (SD 6·4) *vs* 11·9 (SD 7·0) (median 3·6 *vs* 10·2) pg/mg protein; endothelin-1: 4·9 (SD 2·4) *vs* 8·8 (SD 4·9) (median 4·7 *vs* 9·4) pg/mg protein; endothelin-2: 0·9 (SD 0·4) *vs* 0·8 (SD 0·3) (median 0·9 *vs* 0·7) pg/mg protein; endothelin-3: 16·5 (SD 14·2) *vs* 15·4 (SD 8·3) (median 10·5 *vs* 12·9) pg/mg protein. Plasma levels of endothelin-1 did not differ between pre-eclamptic and normal pregnant women [0·48 (SD 0·53) *vs* 0·40 (SD 0·22), median: 0·25 *vs* 0·4 pg/ml, Fig. 3]; the point estimate of the difference between median values was 0·01 pg/ml and the 95% CI was −0·09 pg/ml to 0·20 pg/ml. In contrast, urinary excretion of endothelin-1 was significantly decreased in pre-eclampsia compared with normal pregnancy, both as the absolute excretion rate [139·5 (SD 88) *vs* 303·3 (SD 132·2), median: 105·6 *vs* 271·7 pg/h, $P<0{\cdot}02$] or if calculated for urine creatinine [5·5 (SD 5·6) *vs* 17·8 (SD 8·1), median 4·0 *vs* 15·7 pg/mg creatinine, $P<0{\cdot}02$] (Fig. 4). To investigate if the reduced urinary excretion of endothelin-1 might be due to decreased renal synthesis of its precursor, we measured the urinary excretion of big-endothelin-1. The absolute big-endothelin-1 urinary excretion was comparable in pre-eclampsia and in normal pregnancy [1981·6 (SD 1135·7) *vs* 1517·8 (SD 949·7), median 1981·6 *vs* 1257·5 pg/h]. Big-endothelin-1 urinary excretion, expressed

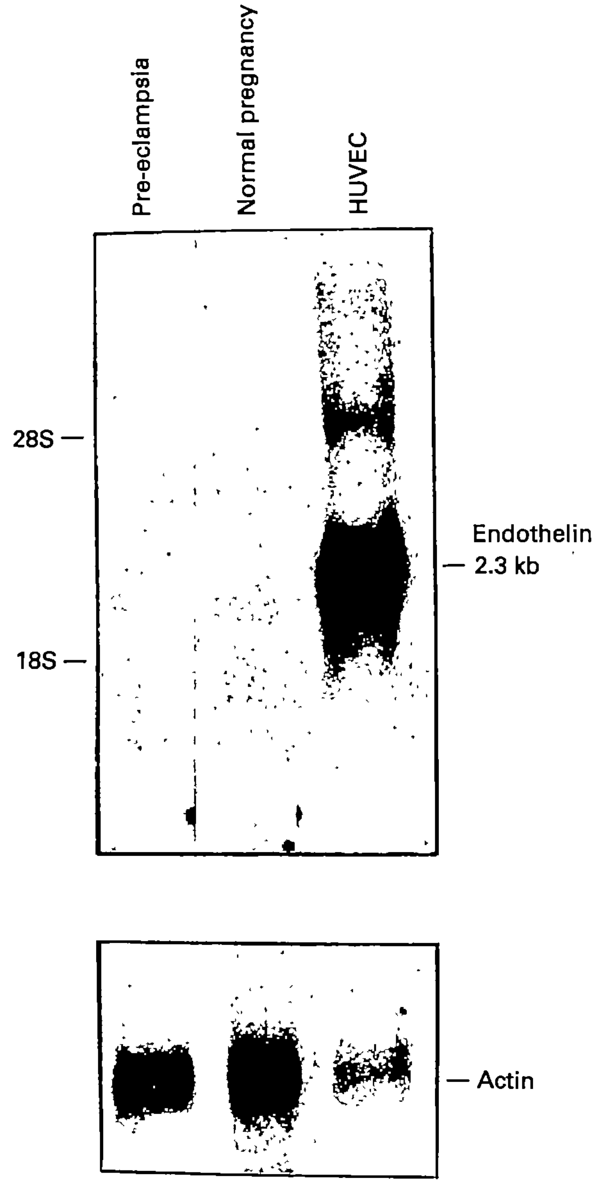

Fig. 1. (Upper panel) Preproendothelin-1 mRNA expression in placental tissue from pre-eclampsia and normal pregnancy. Total RNA from umbilical vein endothelial cells (HUVEC) was used as a positive control. HUVEC ribosomal RNA (28 s and 18 s) was used as a size marker.

(Lower panel) The same membrane was hybridised to the α-actin probe and used as an internal standard of equal loading of the placental samples on the membrane.

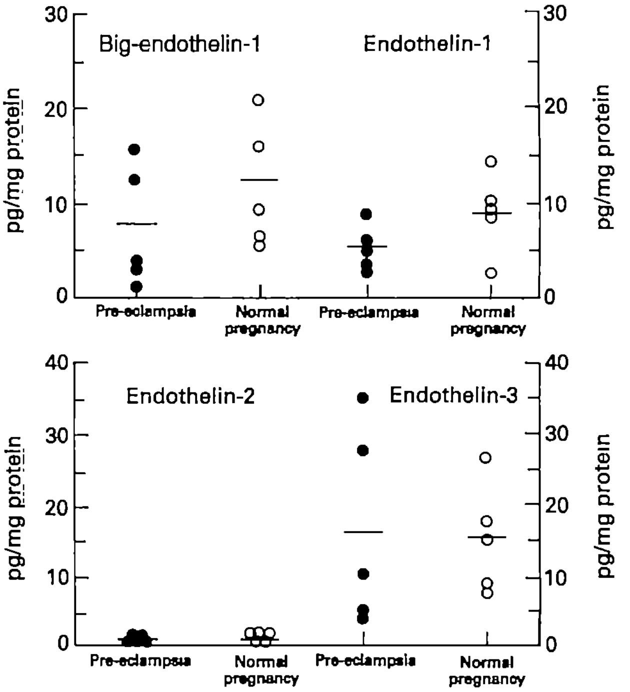

Fig. 2. Immunoreactive big-endothelin-1, endothelin-1, endothelin-2 and endothelin-3 in placentas from five pre-eclamptic and six normotensive pregnant women Horizontal bars are mean values. The characteristics of the women are reported in Table 2.

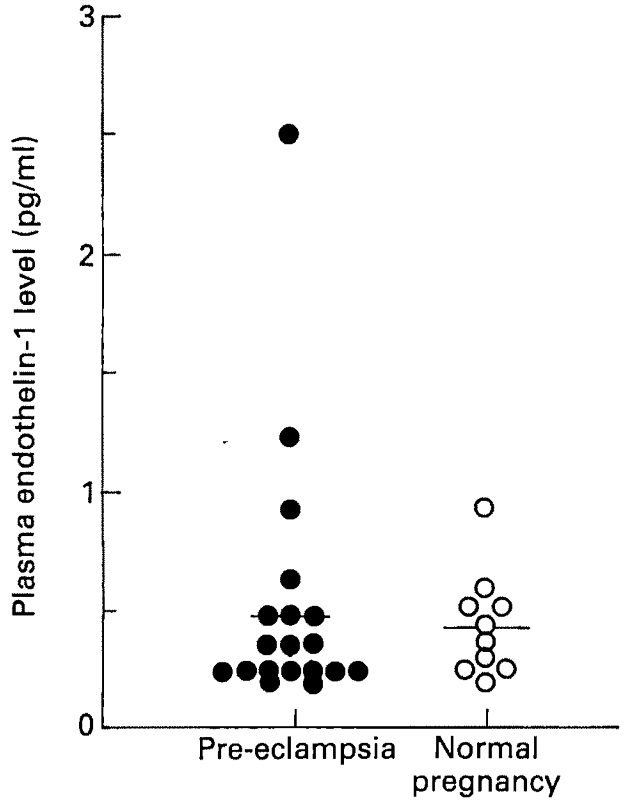

Fig. 3. Plasma endothelin-1 levels measured at term in 19 pregnant women with pre-eclampsia and in 10 normotensive pregnant controls. Horizontal bars are mean values.

per mg urinary creatinine, tended to be lower in pre-eclamptic than in normal pregnancy, although the difference was not statistically significant [91·2 (SD 65·3) *vs* 65·7 (SD 47·6), median 84·2 *vs* 63·9 pg/mg creatinine] (Fig. 5).

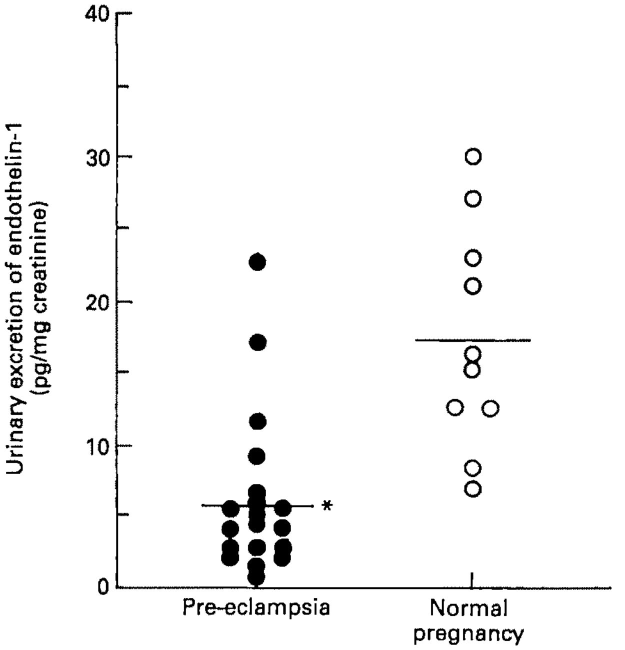

Fig. 4. Urinary excretion of endothelin-1 in 19 women with pre-eclampsia and in 10 normotensive pregnant controls. Horizontal bars are mean values. *$P<0·01$

Discussion

The first finding of this study is that placental tissue from pre-eclamptic women expresses the preproendothelin-1 gene. The transcript was identical in size to that found in placentas from normal pregnant women. The second finding is that placental tissue generates the corresponding peptides and particularly big-endothelin-1, endothelin-1, endothelin-2 and endothelin-3 in amounts which were similar in normal and pre-eclamptic pregnancies. Plasma levels of endothelin-1 were also comparable in normal pregnancy and pre-eclampsia.

Conflicting results have been reported on endothelin plasma levels in pregnant women with hypertension. Some authors observed decreased plasma endothelin levels in women with hypertension and proteinuria (Schrader *et al.* 1990), and recent reports showed significantly higher plasma endothelin levels in women with pregnancy-induced hypertension compared with normotensive pregnant women (Kamoi *et al.* 1990; Taylor *et al.* 1990; Nova *et al.* 1991). Our finding that endothelin-1 plasma levels are similar in normal pregnancy and pre-eclampsia is not surprising in view of the very short half-life of the peptide (Anggard *et al.* 1989) and is consistent with recent data showing that plasma levels of endothelin-1 did not differ between patients with essential hypertension and normotensive controls (Hoffman *et al.* 1990). We extended our studies on endothelin synthesis in pregnancy-induced hypertension to the urinary excretion of the peptide. Previous studies in experimental animals have indicated that the presence of endothelin-1 in the urine reflects its renal synthesis rather than events in the systemic circulation (Benigni *et al.* 1991b; Heublein *et al.* 1990). Within the limits of the above mentioned assumption, the present data that urinary endothelin-1 is significantly decreased in

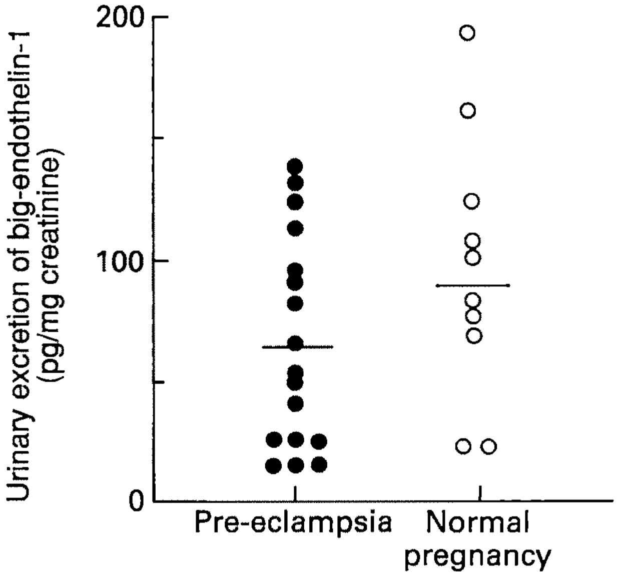

Fig. 5. Urinary excretion of big-endothelin-1 in 19 women with pre-eclampsia and in 10 normotensive pregnant controls. Horizontal bars represent mean values.

pre-eclampsia compared with normal pregnancy might be taken to indicate a decreased renal synthesis. However, failure to demonstrate a reduction in the amount of big-endothelin-1 excreted in the urine in pre-eclampsia rather suggests an enhanced renal breakdown, possibly via enhanced neutral endopeptidase 24·11 activity (Vijayaraghavan *et al.* 1990). Unfortunately experiments to verify whether endopeptidase 24·11 activity is increased in pre-eclampsia are not feasible *in vivo* in humans and no reliable experimental models of pre-eclampsia are available that can be used for this purpose. Altogether the present results do not support a pathogenetic role for endothelin in pregnancy-induced hypertension. This conclusion supports recent findings that pre-eclamptic serum may accelerate the degradation of endothelin *in vitro* (Branch *et al.* 1991). Whether the increased renal endothelin breakdown, which may occur in pre-eclampsia, has the effect of limiting the negative effects of other vasoactive factors (Baylis *et al.* 1980) on the renal circulation is a possibility that needs further investigation.

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OBSTETRICS

Pregnancy induced hypertension and sodium pump function in erythrocytes

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ABSTRACT

Objective To determine if erythrocyte sodium pump function is altered with the onset of pregnancy induced hypertension.

Design A prospective descriptive study.

Subjects Thirty-two primigravid women with pregnancy-induced hypertension (17 had proteinuria) and 32 gestation-matched normotensive primigravid pregnant women were studied and measurements repeated 20 weeks after delivery.

Intervention Erythrocyte sodium, ouabain-sensitive sodium flux and the sodium pump rate constant were measured in whole blood and the maximum velocity and sodium affinity of the sodium pump were measured *in vitro*.

Results Blood pressure remained higher after delivery in the women who had been hypertensive during pregnancy. In normal pregnancy erythrocyte sodium was decreased, and ouabain-sensitive sodium flux, the sodium pump rate constant and maximum velocity (V_{max}) were increased compared with 20 weeks after delivery. In pregnancy-induced hypertension erythrocyte sodium and sodium pump changes were the same as in normal pregnancy. The possibility of a positive association between changes in erythrocyte sodium and in blood pressure was excluded. The rate constant of the sodium pump in blood was related to its V_{max} measured *in vitro* but the relation had greater variance in the hypertensives with 7 of the 32 women having rate constants greater than expected from their V_{max}.

Conclusion There was no evidence of sodium pump inhibition or a rise in intracellular sodium associated with increased blood pressure in pregnancy. There may have been stimulation of the sodium pump by a plasma factor in some hypertensive women.

There has been much interest in intracellular sodium and sodium pump activity in relation to essential hypertension and the erythrocytes of hypertensive subjects have been used as a model for study (Trevisan *et al.* 1983; Garay & Meyer 1979). The most popular hypothesis is that a sodium pump inhibitor is produced, possibly in response to extracellular volume expansion, causing increased intracellular sodium (Blaustein 1977; De Wardener & McGregor 1980), increased neuromuscular excitability and hence increased vascular wall tone. Attempts to demonstrate this increased erythrocyte sodium in essential hypertension have given conflicting results (Simon & Conklin 1986) possibly because of relatively large inter-subject variations (Smith 1972).

Hypertension is common in pregnancy and a major cause of maternal and fetal morbidity. As it usually resolves after delivery comparisons can be made within individuals. The involvement of a sodium pump inhibitor in the pathogenesis of pregnancy-induced hypertension (PIH) has been examined (Phelps *et al.* 1988; Poston *et al.* 1989; Gusdon *et al.* 1984; Gregoire *et al.* 1988; Kerkez *et al.* 1990), but the intrinsic kinetic behaviour of the erythrocyte sodium pump in hypertensive pregnancy compared with normal pregnancy and its relation to the control of intracellular sodium has not been investigated previously.

We have therefore studied women with pregnancy-induced hypertension and gestation-matched normal pregnancies both during pregnancy and 20 weeks post delivery. Erythrocyte sodium and sodium pump activity were measured in whole blood under conditions near to those *in vivo* and sodium pump kinetics were measured in a plasma-free incubation buffer (Thomas *et al.* 1990).

Subjects and methods

Thirty-two primigravid women with pregnancy-induced hypertension were recruited following admission to the antenatal ward for assessment. All had elevations in diastolic blood pressure (Korotkoff IV) sustained above 90 mmHg over a 24 h period and none had previously received any

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form of anti-hypertensive medication. Proteinuria was quantified in a 24-h collection where possible and considered significant if more than 0·5 g was excreted in 24 h. If there was insufficient time for a 24 h collection, +++ on urine dipstick testing was considered to be significant. All women were also studied 20 weeks after delivery.

Thirty-two normotensive primigravid pregnant women were selected from a longitudinal study where all women were studied every 6 weeks between 14 and 38 weeks' gestation (Macphail *et al.* 1990). All were investigated again at 20 weeks after delivery. Pregnant women from this group were matched for gestation, age and body weight with women who had hypertensive pregnancies.

This study had the approval of the joint ethics committee of Newcastle Health Authority and the University of Newcastle upon Tyne. Verbal consent was obtained from all subjects.

Measurements in whole blood

Blood was collected from an antecubital vein into tubes containing lithium heparin. The methods used were as described by Thomas *et al.* (1990). In brief, the blood was centrifuged at 2000 *g* for 5 min at 4°C, the plasma discarded and the erythrocytes washed three times with $MgCl_2$ (289 mosmol/kg). Erythrocytes were then centrifuged in 6 × 45 mm polythene tubes at 15 000 *g* for 15 min at room temperature in a fixed angle head (Murphy 1973). The top 7–10% of the erythrocyte column was removed, weighed and disrupted in 1·5 mmol/l CsCl and sodium was measured on an IL 943 flame photometer (Instrumentation Laboratory, Warrington, Cheshire, UK). Sodium was calculated as mmol/kg wet cell mass and the assay had a coefficient of variation of 2·3%.

Ouabain-sensitive sodium flux was measured by incubating 1·5 ml of blood with 10^{-4} mol/l ouabain for 2 h (Cumberbatch & Morgan 1978) and measuring erythrocyte sodium as above. Ouabain-sensitive sodium flux was the increase in erythrocyte sodium in the presence of ouabain (mmol h^{-1} kg^{-1} wet weight cells) and the assay had a coefficient of variation of 2·7%. The sodium pump rate constant (h^{-1}) was calculated from the equation:

ouabain-sensitive sodium flux = rate constant × erythrocyte sodium

Measurement of sodium pump kinetics

Sodium pump flux was measured at three different erythrocyte sodium contents, one being the original sodium content and two others achieved using the ionophore nystatin at 4°C for 30 min in the presence of media with different sodium contents (in mmol/l: 22·5 NaCl + 127·5 KCl and 82·5 NaCl + 67·5 KCl; both with 1 $MgCl_2$ and 10 Tris-acetate pH 7·4 and 50 or 100 mg/l respectively nystatin). Erythrocytes were washed once with the same solution without nystatin but containing albumin (1 g/l) and three times with $MgCl_2$ (289 mosmol/kg).

Sodium efflux was determined from the increase in sodium content of a sodium-free medium (in mmol/l: 139 choline chloride, 5 KCl, 1 $MgCl_2$, 10 glucose, 10 Tris-acetate, pH 7·4, 290 mosmol/kg) during incubation with erythrocytes for 1 h at 37°C. The sodium pump flux rate was the difference between efflux in the presence and absence of 10^{-4}mol/l ouabain. Each cycle of the sodium pump requires three sodium ions to be bound to the enzyme so that the relation between activity (sodium flux rate) and the maximum velocity (V_{max}) and the sodium affinity constant (k_m) is given by:

$$\text{flux} = V_{max}/\,(1 + k_m/\text{Na})^3$$

(Garay & Garrahan 1973). For the calculation of V_{max} and k_m this can be rearranged as:

$$\text{flux}^{1/3} = V_{max}{}^{1/3} - (\text{flux}^{1/3}/[\text{Na}^+]_i)k_m$$

Plotting $\text{flux}^{1/3}$ against $\text{flux}^{1/3}/[\text{Na}^+]_i$ gave k_m from the slope of the line and $V_{max}{}^{1/3}$ was the intercept with the y-axis (Thomas *et al.* 1990). The median coefficient of variation for V_{max} and k_m from individual plots was approximately 20% and with 32 subjects in each group allowed differences in V_{max} and k_m of 1 mmol/h/kg cells and 0·4 mmol/l respectively to be detected with $P = 0{\cdot}05$ and a power of 80%. This is approximately half of the standard deviation of the individual change due to normal pregnancy. The statistical power for the other erythrocyte variables was similar.

Statistical analyses

Differences between pregnant and postnatal values were assessed using Student's *t* test for paired samples and between hypertensive and normotensive women using the unpaired *t* test. The relation between variables was assessed using the Pearson correlation coefficient. Variances were compared using the *F* test.

Results

The women who became hypertensive during pregnancy were compared with normotensive pregnant women matched primarily for stage of gestation as well as age and body weight (Table 1). Both the systolic and diastolic blood pressures were higher in the hypertensive women and were still elevated 20 weeks after delivery compared with the women who had had normotensive pregnancies (Table 1). However, the differences in blood pressure between pregnant and postnatal measurements were greater in the women with pregnancy-induced hypertension. Seventeen of the hypertensive pregnant women had proteinuria of more than 0·5 g/24 h (mean 2·21 g/24 h, SE 0·59) but this was not related to any of the other observations.

The normotensive women had a significant reduction in erythrocyte sodium and increase in ouabain-sensitive sodium flux and sodium pump rate constant during pregnancy compared with values 20 weeks after delivery (Table 2). The increased rate constant was due to an increased maximum velocity (V_{max}) of the sodium pump during pregnancy with no difference in the sodium affinity constant (k_m). The hypertensive pregnant women had a similar decrease in erythrocyte sodium and increases in ouabain-sensitive sodium flux, sodium pump rate constant and maximum velocity compared with their values 20 weeks after delivery. There were no significant differences in erythrocyte sodium, sodium pump flux, sodium pump rate constant or sodium pump kinetics between

Table 1. Characteristics of the women in the study groups.

Variable	Pregnancy-induced hypertension (n = 32)	Normotensive (n = 32)
Gestation (days)	254·6 (19·5)	255·3 (21·6)
Age (years)	27·2 (1·0)	28·8 (4·0)
Body weight (kg)	58·7 (8·9)	60·6 (7·3)
Systolic BP (mmHg)		
Pregnant	143·7 (15·0)*	114·2 (8·2)
Postnatal	118·3 (13·4)*†	108·5 (7·6)†
Diastolic BP (mmHg)		
Pregnant	97·1 (6·1)*	76·1 (7·5)
Postnatal	80·1 (9·4)*†	72·6 (7·4)†

Results are mean (SD) values.
Significance of difference between hypertensive and normal pregnancies *P<0·001, and between pregnant and postnatal values in the same study group †P<0·001.

the hypertensive and normotensive pregnant women either when pregnant or 20 weeks after delivery. The decrease in erythrocyte sodium and the increases in ouabain-sensitive sodium flux, rate constant and maximum velocity associated with pregnancy in the hypertensive women were not significantly different from the changes seen during pregnancy in the normotensive women (Table 2).

Erythrocyte sodium was similar in the hypertensive and normotensive pregnancies. In the normotensive pregnant women there was no significant correlation either between erythrocyte sodium and mean arterial pressure (MAP) (r = –0·30; 95% CI –0·59 to 0·06; P = 0·10) or between the pregnant to post-natal changes in erythrocyte sodium and MAP (r = –0·06; 95% CI –0·40 to 0·29; P = 0·8). In the hypertensive pregnant women the corresponding values were r = 0·08 (95% CI –0·28 to 0·42; P = 0·7) and r = –0·17 (95% CI –0·49 to 0·29; P = 0·4). With the values for normotensive and hypertensive women combined the values were r = –0·15 (95% CI –0·47 to 0·21; P = 0·25) and r = –0·02 (95% CI –0·37 to 0·33; P = 0·9) respectively. Although these relations are not statistically significant, they make a positive correlation between sodium content and blood pressure very unlikely.

Of the kinetic indices, V_{max} was closely related to the rate constant of the sodium pump in the normotensive pregnant women but there was no relation with k_m. The correlations between the rate constant of the sodium pump and V_{max} were similar in the normotensive and hypertensive pregnant women (Fig. 1). However, 7 of the 32 hypertensive women had a rate constant more than 2 SE greater than predicted from V_{max} by the relation in normotensive women. In addition, the variance of the estimate of the rate constant from V_{max} was significantly greater in the hypertensive than in the normotensive women (F = 5·24, P<0·01).

Discussion

We have previously described in detail the changes in erythrocyte sodium and the sodium pump in a longitudinal study during normal human pregnancy (Macphail *et al.* 1990). This showed that erythrocyte sodium decreased and the sodium pump rate constant increased up to 26 weeks' gestation with no further significant change thereafter. After 20 weeks' gestation the raised sodium pump rate constant was maintained by an increasing maximum velocity (V_{max}) of the sodium pump. These findings are compatible with those in the present study which involved the use of data from a cohort of the same women as normal control data, appropriately matched for gestation, age and body weight for comparison with the hypertensive pregnant women.

Table 2. Erythrocyte sodium pump function in pregnancy-induced hypertension compared with normotensive pregnancies.

	Pregnancy-induced hypertension (n = 32)		Normotensive (n = 32)	
Variable	Pregnant	Postnatal	Pregnant	Postnatal
Erythrocyte $[Na]_i$ (mmol/kg cells)	3·87 (0·13)	4·84 (0·15)	4·07 (0·09)	5·10 (0·12)
Ouabain-sensitive sodium flux (mmol/h/kg cells)	1·79 (0·04)	1·64 (0·04)	1·76 (0·03)	1·58 (0·02)
Sodium pump				
Rate constant (h^{-1})	0·48 (0·02)	0·35 (0·01)	0·44 (0·01)	0·32 (0·01)
Sodium affinity constant (mmol/l)	2·74 (0·12)	2·75 (0·10)	2·92 (0·07)	2·74 (0·12)
Maximum velocity (mmol/h/kg cells)	9·06 (0·47)	7·17 (0·31)	9·10 (0·29)	6·31 (0·23)

Results are mean (SEM) values.
There were significant differences (P<0·001) in both groups between pregnant and postnatal values for all variables except sodium affinity constant.

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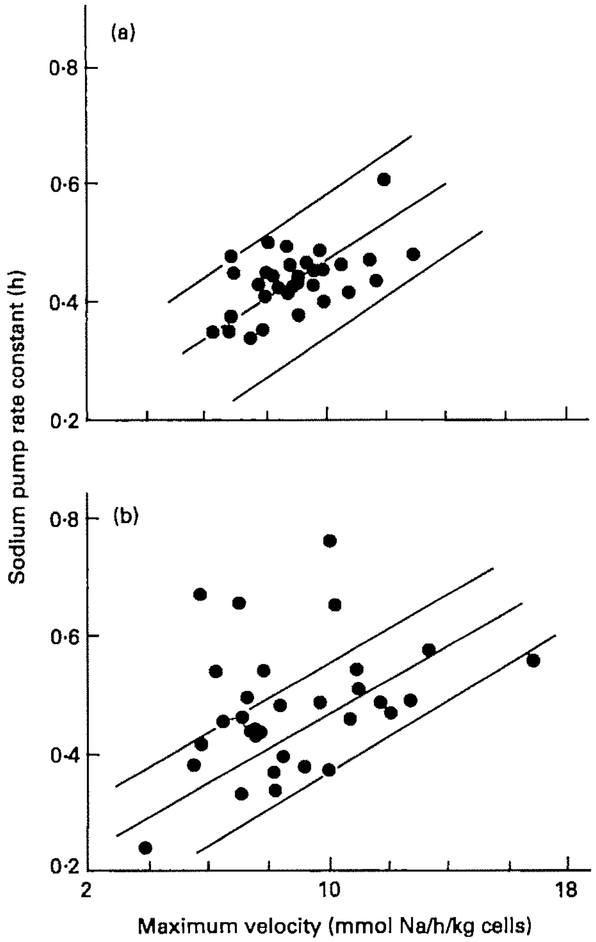

Fig. 1. The relation between the sodium pump maximum velocity measured *in vitro* and the rate constant measured in blood in (a) normotensive ($r = 0{\cdot}54$, $P = 0{\cdot}002$) and (b) hypertensive (r–0·33, $P = 0{\cdot}07$) pregnancies. The y on x regression line and 2 SE of the estimate of y from x for the normotensive women is shown on both plots.

There were no differences in erythrocyte sodium, sodium pump flux, rate constant or kinetics between pregnant women who were normotensive and those who became hypertensive during pregnancy. In both cases, pregnancy had a similar effect in lowering erythrocyte sodium by increasing available sodium pump activity by an increase in maximum velocity.

There were no statistically significant relations between either erythrocyte sodium and blood pressure or the changes in erythrocyte sodium and blood pressure associated with normotensive pregnancy. However, as both blood pressure and erythrocyte sodium fall progressively in normal pregnancy, a positive correlation is unlikely. It is also unlikely that any circulating digoxin-like substance plays any functional role during normal pregnancy (Vinge *et al.* 1988; Gonzalez *et al.* 1987; Phelps *et al.* 1988; Graves *et al.* 1984; Kerkez *et al.* 1990; Morris *et al.* 1988). If hypertension was an extension of the normotensive range of blood pressure then combining both groups should have increased the correlation coefficient of any association simply by extending the range of values. This did not happen for erythrocyte sodium and blood pressure, even for the negative correlation, suggesting that hypertension was not an extension of the relation in normal pregnancy. The absence of a positive correlation between erythrocyte sodium and blood pressure suggests that the popular hypothesis relating raised intracellular sodium to hypertension does not apply in pregnancy. Therefore, the data from the present study suggest that there is no evidence of a functional sodium pump inhibitor or an increase in intracellular sodium as factors in pregnancy-induced hypertension. The present data are in greater accord with the challenge to the hypothesis that raised intracellular sodium is a cause of hypertension (Simon & Conklin 1986). The erythrocyte is not a model of vascular smooth muscle since it lacks the specific cell structures and some of the ion-flux mechanisms characteristic of muscle action. It does provide a model of some general processes of the control of cell ion balance. An alteration in such processes is likely to be widespread but, in smooth muscle, could result possibly in an increase in tone. In the present study, measurements of cell sodium content and net flux were made with very little disturbance from the *in vivo* state which may be of considerable importance (Simon & Conklin 1986).

Although the relation between intracellular sodium concentration and sodium pump activity is approximately first order within the physiological range, the use of a rate constant to assess sodium pump status has been criticised on theoretical grounds, since it may obscure differences in sodium affinity and maximum velocity which both independently affect the rate constant (Aronson 1990). However, in erythrocytes from normal non-pregnant subjects, the rate constant does relate to sodium affinity and maximum velocity and gives an estimate of available sodium pump activity (Thomas *et al.* 1990). In addition, the sodium pump rate constant in erythrocytes can be measured in whole blood in conditions close to those *in vivo*. When the rate constant and the estimates of sodium affinity and maximum velocity made under *in vitro* conditions do not agree, it seems likely that conditions *in vitro* have affected sodium pump function. This phenomenon was observed previously during the second trimester of normal pregnancy (Macphail *et al.* 1990).

In the present study, during pregnancy, the sodium pump rate constant in blood was significantly correlated with the V_{max} measured *in vitro* in both normotensive and hypertensive women. However, 7 of the 32 hypertensive women had a rate constant that was more than 2 SE of the estimate of rate constant from V_{max} in the normotensives (Fig. 1) and none had a value less than 2 SE of the estimates. This suggests that in the hypertensive women the sodium pump was tending to be more active in the presence of plasma and is further evidence against an effective sodium pump inhibitor in plasma but does suggest that sodium pump function is altered when pregnancy is complicated by hypertension.

Although normotensive 20 weeks after delivery, the women who had been hypertensive during pregnancy continued to have a higher mean blood pressure than the women who had been normotensive during pregnancy. This suggests that there may have been an underlying tendency to essential hypertension in the women who had hypertension apparently induced by pregnancy. However, there were no corresponding differences in the postnatal erythrocyte values.

In conclusion, there was no evidence from the present study that an increase in intracellular sodium was associated with pregnancy-induced hypertension. However, it did appear that in some women the loss of appropriate control of blood pressure was associated with a disturbance in the control of sodium pump activity.

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OBSTETRICS

Previous miscarriage and stillbirth as risk factors for other unfavourable outcomes in the next pregnancy

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ABSTRACT

Objective To look for associations between previous fetal loss and fetal malformation or low birthweight in a subsequent pregnancy.

Design A case-control study with place of birth, time and sex matched controls.

Setting 72 South American maternity hospitals.

Subjects 18 534 malformed, 1150 non-malformed babies of low birthweight and 16 394 controls. All babies were from mothers with at least one previous pregnancy.

Main outcome measures Frequency of stillbirths and miscarriages in the previous pregnancy and outcome of the index pregnancy.

Results Multiple malformation, Down's syndrome, anencephaly, spina bifida, pes equinovarus, congenital dislocation of the hip and low birthweight are associated with previous fetal loss.

Conclusion A miscarriage or a stillbirth in a previous pregnancy should be taken into account when the risk of malformations or low birthweight in a subsequent pregnancy is assessed.

Most human beings die before birth; only about one-third of all conceptions reach the first year of life (Opitz 1987).

Most conceptions are lost during the preclinical stage of gestation and the women are unaware they have occurred (Tinneberg *et al.* 1985; Wilcox *et al.* 1988). Nevertheless, the frequency of miscarriage and stillbirth after clinical recognition of pregnancy is still large enough to allow case-control or cohort studies (Ferraz & Gray 1991; Hogston & James 1990; Tan *et al.* 1989; Alessandri *et al.* 1988).

There are four generally accepted manifestations of abnormal intrauterine development: death, malformation, growth retardation and functional deficit (Wilson 1980). During pregnancy, these lethal and non-lethal developmental anomalies can be considered, at least in some cases, as part of a single phenomenon.

It is known that embryonic and fetal death can be associated in successive pregnancies. However, the relation between pregnancy wastage and the occurrence of other unfavourable outcomes in a subsequent pregnancy is still controversial.

The association of miscarriage with fetal pathology in successive pregnancies has been suggested: with congenital anomalies, low birthweight and low Apgar scores (Farber *et al.* 1984; Thom *et al.* 1992), with Down's syndrome and low maternal age (Hook & Cross 1983), or with intrauterine growth retardation and immaturity (Miller & Jekel 1985).

If it is accepted that traits severely affecting the phenotype and jeopardising survival can act either pre- or post-natally, then the successive pregnancies of women affected by such traits could be expected to show a higher rate of prenatal loss than those of women having normal or mildly affected children.

The purpose of this study was to look for associations between previous fetal loss and malformation or low birthweight in the subsequent pregnancy, controlling for several genetic and environmental variables.

Subjects and methods

In the period 1967–1986, a total of 1 072 911 liveborn infants were examined (547 219 males, 524 177 females and 1515 of undetermined sex) by the Latin-American Collaborative Study of Congenital Malformations (ECLAMC), following a standard methodology (Castilla *et al.* 1974).

Specially trained paediatricians associated with the 72 South American maternity hospitals participating in the study completed a form for each malformed livebirth diagnosed during the first 72 h of life. The same was done for a control infant, defined as the next non-malformed livebirth in the hospital and paired by sex.

Specific instructions for unusual events, such as consecutive infants with malformation, twins and infants of undetermined sex were included in the instruction manual for the study.

From 1982, stillbirths were included and 8318 (4449 males, 3623 females and 246 of undetermined sex) were examined and forms were completed for those with malformations.

There was a total of 28 236 malformed livebirths (2·63%) and a similar number of controls.

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Table 3. Correlation coefficients between fetal arterial systolic/diastolic Doppler (A/B) ratios and umbilical vein blood gas components.

	A/B ratio measured in					
	Internal carotid artery		Thoracic aorta		Abdominal aorta	
Umbilical vein blood component	*r*	*P*	*r*	*P*	*r*	*P*
PO_2	0·01	0·89	−0·11	0·32	0·02	0·87
PCO_2	0·01	0·92	−0·05	0·67	−0·07	0·52
O_2-content	0·08	0·49	−0·09	0·43	0·03	0·80
CO_2-content	0·13	0·27	0·19	0·87	−0·07	0·51
HCO_3	0·11	0·36	0·02	0·88	−0·12	0·27
Base excess	0·10	0·39	−0·06	0·57	−0·11	0·30
Lactate	0·01	0·74	0·12	0·28	0·04	0·74

vein blood gases or lactate concentration. The correlation coefficients and *P*-values between the A/B ratios and umbilical vein blood gas components are shown in Table 3 and Figure 1 shows the relation between the A/B ratio in the three fetal arteries and the umbilical vein blood oxygent content.

The ratio between the Doppler indices from the different vessels (value of the index from one vessel/value of the same index from an other vessel) was also independent of the blood gases and the acid-base status and there was no significant difference between the Doppler indices in the same vessel in fetuses with blood gases in the upper quartile compared with the lower.

Discussion

Our study includes a wide range of blood gas values from normal, hypoxaemic and acidotic fetuses. We found no relations between the blood gases and the Doppler indices in any of the examined vessels. The close correlation in erythroblastotic fetuses between haemoglobin concentration and both base excess and lactate reported previously (Westgren *et al.* 1989) was confirmed. The increased concentration of lactate and the decreased base excess in umbilical vein blood of the anaemic fetuses is most likely due to a shift to anaerobic metabolism caused by insufficient oxygen delivery to peripheral tissue.

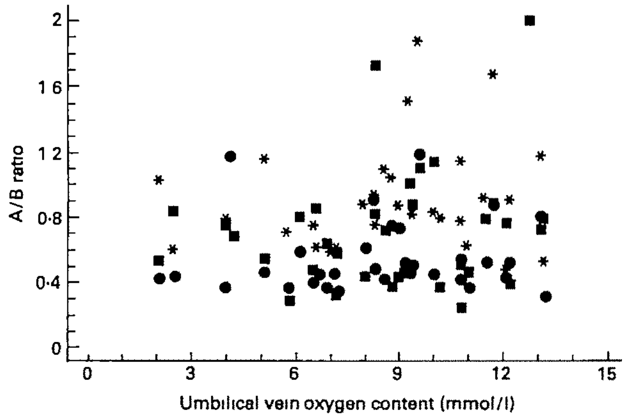

Fig. 1. Plot of the systolic/diastolic ratio (A/B) from the thoracic aorta (*) abdominal aorta (●) and the internal carotid artery (■) on the oxygen content of the umbilical vein. No significant correlations were found

Studies on pregnant ewes (Peeters *et al.* 1979) subjected to inhalation of gas mixtures containing from 10 to 100% oxygen have shown that fetal cerebral blood flow increases in inverse relation to arterial O_2 content. In a study of 81 small-for-gestational age (SGA) human fetuses a significant positive relation was found between PI in the middle cerebral artery and PO_2 in the umbilical vein (Vyas *et al.* 1990).

The erythroblastotic fetuses in the present study had an impaired oxygen delivery capacity that was independent of PO_2. This lack of correlation between PO_2 and oxygen delivery capacity in these fetuses might explain the difference between our results in anaemic fetuses and other studies in SGA fetuses (Vyas *et al.* 1990; Lingman & Maršál 1989). If the tonus of the fetal cerebral vessels is dependent on receptors sensitive to PO_2 but insensitive to oxygen delivery capacity and the other blood gas features, this would explain why the ratio between the Doppler indices from the four vessels in our study were independent of the blood gases and acid-base status.

The blood flow in different vessels follows the Poiseuille formula:

Flow = Perfusion pressure/Resistance

A close linear correlation has been demonstrated between the vascular resistance and both the A/B ratio and the PI (Legarth & Nolsoe 1990). In our study the resistance as measured by Doppler was independent of the fetal blood gases components. A change in the fetal blood pressure related to asphyxia could change the perfusion pressures (the mean arterial pressure — the venous pressure). An elevation of the blood pressure would increase the blood flow to the fetal organs and could secure the oxygen supply to the brain in the erythroblastotic fetus. In our study the resistance was independent of the fetal blood gas components, and a change in blood pressure would therefore have the same impact on blood flow to all vessels Thus, no redistribution of blood flow (classic brain sparing effect) was demonstrated.

Haemodynamic factors other than vascular resistance can also modify low velocity waveform in the anaemic fetus. In a study (Lingman *et al.* 1991) concerning cardiac performance in erythroblastotic fetuses we have reported previously that the blood acceleration in systole and the maximum blood velocity in the ascending aorta were inversely correlated to haemoglobin concentrations higher than 65 g/l. Below that level there was a decrease in blood acceleration. Furthermore, a second-power relation was found between the umbilical artery PI and the blood acceleration in the fetal ascending aorta, with the highest PI values found in fetuses with the lowest haematocrit and cardiac contractility. A similar relation between the cardiac performance and the Doppler indices in the internal carotid artery could make a decrease in the Doppler indices otherwise created by a vasodilatation as a response to hypoxia. But such an effect of the cardiac performance on the blood flow velocity waveform would influence the Doppler indices in all the vessels and should not change the relation between the indices from the different vessels. So an eventual redistribution of the blood circulation is not likely to have been masked by change in the cardiac performance.

We conclude that this study does not support a reduction in peripheral vascular resistance in the fetal cerebrum in relation to hypoxia in fetuses of rhesus immunized pregnancies.

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The form included the following data relevant to this study: hospital, date of birth, sex, birthweight, twinning, phenotypic description (only for the malformed), date of last menstrual period, maternal age, maternal disease classified as chronic, when starting before or during the first trimester of pregnancy and still present at the moment of the interview, or acute when starting and ending during the first trimester (excluding vomiting or threatened miscarriage), previous infertility, the full pedigree of the family if there was parental consanguinity, ethnic group, the educational attainment of both parents and the occupation of the father using an 8-point scale.

The result of all the pregnancies of the woman were recorded for every case, and the woman was told that the questions about prenatal deaths referred only to miscarriages and stillbirths and excluded induced abortions. Ectopic pregnancies were counted as miscarriages.

The outcome of the pregnancy previous to the proband was categorised as livebirth, stillbirth or miscarriage.

Among the livebirths with malformation 9940 (35·2%) resulted from a first pregnancy and they were excluded, 82 with anencephaly and six with Down's syndrome that were stillborn were added, giving a total of 18 384. Of the remaining 343 malformed stillbirths, 193 were excluded because they occurred in a first pregnancy, giving a total of 150 malformed stillbirths.

Of the 28 236 control infants, 10 692 (37·9%) resulting from a first pregnancy were excluded. Of the remainder, 1150 had a birthweight lower than 2500 g (LBW); 668 of these were small for gestational age (Sanders & James 1985) and were classified as LBW-SGA. The other 482 were classified as of low birthweight appropriate for gestational age (LBW-AGA). After these reclassifications the control consisted of 16 394 livebirths with birthweights ≥2500 g.

Single malformations or recognised syndromes of which more than 100 cases occurred were grouped in the following categories: Down's syndrome, anencephaly, spina bifida, cleft lip with or without cleft palate, hypospadias, polydactyly, pes equinovarus, pes talovalgus, and congenital dislocation of the hip (Ortolani's positive sign). Other infants with single malformations and with multiple malformations constituted two additional categories.

Length of gestation was calculated as complete weeks from the last menstrual period to the birth date. A socioeconomical indicator was calculated by adding the scores of educational attainment of both parents and the occupational score for the father, dividing by 3 and rounding to the nearest integer. If data for the father were not specified, the score for mother's educational attainment was used as the socioeconomical indicator. The interval between pregnancies was calculated in completed weeks from the end of the previous pregnancy to the case birthdate. The previous infertility was recorded as yes or no. For the logistic regression maternal age was dichotomised at <35 years, the interval between both pregnancies at <34 weeks and socioeconomical level at <4.

The χ^2 test with Yates' correction was used to compare proportions.

After the elimination of twins, a linear logistic regression analysis was performed for each group against the control group, using the result of the previous pregnancy as independent variable and controlling for seven confounders: socioeconomic level, interval between both pregnancies, parental consanguinity, maternal age, chronic and acute diseases and previous infertility. Odds ratios were calculated from the multiple logistic regression analysis as e^b, where b is the regression coefficient. The attributable fraction was calculated using the frequency of the risk factor among cases and the odds ratio (Miettinen 1974).

Results

Table 1 displays a group of variables describing the sample that show good agreement with what was expected for each group: a low sex index for congenital dislocation of the hip and pes talovalgus; high twinning rates for malformed stillbirths, LBW-SGA and LBW-AGA; high frequency of black ancestors with polydactyly. Weight and gestation were part of the definition of LBW-SGA and LBW-AGA and show the expected associations.

Table 2 shows the individual results for all the independent and confounding variables.

Table 3 shows the results of the logistic regression analysis. The differences in the number of cases with Table 1 are due to cases with one or more not-specified variables, that were eliminated for the analysis.

Interaction between independent and confounding variables was analysed in a first step. Only for the Down's syndrome group was an interaction found between previous miscarriage and acute illness, with $P<0{\cdot}05$. Thus, interaction was not included in the final logistic regression analysis.

Odds ratios are presented for the independent variables and the level of significance of z are shown. Only those odds ratios for which z had a $P<0{\cdot}01$ are displayed for the confounding variables.

Table 4 shows the distributions of the confounding variables between cases with and without previous miscarriage or stillbirth, only where a significant association with the independent variable was found. This explains the apparent discrepancies in the number of cases compared with Table 3.

Except for LBW-AGA with previous stillbirth, differences in the interval between pregnancies were significant in all cases. More mothers of babies with Down's syndrome and other single malformations with a previous miscarriage had had previous infertility and chronic diseases than those with a previous livebirth. This was also true in cases with acute diseases in the other single malformed group, these differences being significant at the $P<0{\cdot}05$ level.

Three per cent of cases with congenital dislocation of the hip and miscarriage in the previous pregnancy had true luxation; 36·9% were bilateral, and this proportion was not different from 2·4% and 38·5%, respectively, for cases with a livebirth in the previous gestation.

Among cases with pes equinovarus with miscarriage in the previous pregnancy, 79·5% were irreducible and 56·8% bilateral, and this was not different from 77·4% and 48·8% respectively, for cases with a livebirth in the previous pregnancy.

Discussion

The frequency of miscarriage in the previous pregnancy of

Table 1. Sample description.

Group	*n*	Sex index (M/M+F)	Twinning (%)	Weight (g) mean	(SE)	Gestation length (weeks) Mean	(SE)	Ethnic group: Latin Europeans (1) (%)	Natives (2) (%)	Blacks (3) (%)	1 + 2 (%)	1 + 3 (%)	2 + 3 (%)	Others (%)
Malformed SB	150	0·540	6·0	2224	(98)	34·7	(0·50)	1·6	51·6	0·8	26·2	0·0	7·9	11·9
Multimalformed	2478	0·532	2·7	2945	(15)	38·6	(0·07)	6·9	43·1	1·7	23·7	3·4	10·4	10·8
Down's syndrome	1246	0·491	1·8	2900	(17)	38·2	(0·08)	7·2	41·1	1·0	24·8	3·4	12·8	9·7
Anencephaly	297	0·440	3·7	2217	(54)	37·9	(0·29)	7·0	41·3	1·1	21·8	2·6	13·7	12·5
Spina bifida	212	0·472	3·8	3042	(45)	38·5	(0·24)	5·7	34·0	0·0	26·3	4·1	20·6	9·3
Cleft lip	626	0·585	2·7	3188	(25)	39·1	(0·13)	5·9	48·4	0·4	25·9	2·3	8·2	8·9
Hypospadias	402	1·000	3·5	3169	(32)	39·1	(0·14)	11·9	32·9	2·5	23·2	5·0	13·0	11·5
Polydactyly	1109	0·550	2·3	3264	(17)	39·3	(0·09)	5·9	33·9	5·2	17·6	4·6	23·5	9·3
Pes equinovarus	901	0·607	2·2	3165	(21)	38·9	(0·10)	6·5	38·8	1·6	25·6	3·3	13·5	10·7
Pes talovalgus	230	0·361	2·2	3181	(29)	38·9	(0·18)	6·9	44·6	1·0	27·9	3·4	7·8	8·4
Hip dislocation	1132	0·233	2·0	3355	(15)	39·6	(0·07)	10·3	42·5	1·0	23·5	3·0	7·9	11·8
Other single malformed	9571	0·519	2·1	3251	(6)	39·1	(0·03)	5·3	44·6	1·7	25·2	4·5	8·4	10·3
LBW-SGA	668	0·449	8·8	2032	(16)	37·1	(0·14)	6·8	40·7	2·5	23·7	4·4	10·2	11·7
LBW-AGA	482	0·501	7·6	2017	(28)	32·1	(0·19)	3·7	38·7	2·1	22·7	3·8	9·2	19·8
Controls	16394	0·519	0·6	3337	(4)	39·4	(0·01)	6·7	43·6	1·4	24·6	3·4	10·2	10·0

SB = still birth, LBW = low birthweight (<2500g); SGA = small-for-gestational age, AGA = appropriate for gestational age

cases and controls in our study is in agreement with other retrospective studies of miscarriage (Warburton & Fraser 1964; Jain 1969; Naylor 1974).

The use of only the previous pregnancy rather than the whole reproductive history has the advantage of minimising maternal memory bias, while maximising the probability of detecting single environmental factors acting in both pregnancies. Genetic factors are not influenced by this restriction because they have the same chance of occurring in any of the woman's pregnancies.

Differences in the frequencies of miscarriage and stillbirth between groups could be attributable to maternal memory bias, related to the distress of having had an unfavourable outcome. However, when cases with LBW-SGA were compared with those with LBW-AGA, both of which are rarely recognised by the woman when interviewed medically, LBW-AGA showed a stronger association with miscarriage and stillbirth than LBW-SGA, suggesting that maternal memory bias does not have an important influence on the results.

Our results suggest that fetal losses are associated with other fetal pathologies in successive pregnancies.

Those traits resulting in serious physical impairment, such as multiple malformation, anencephaly, spina bifida, and both groups of low birthweight, are associated with miscarriage or stillbirth, while mild malformations such as cleft lip, hypospadias, polydactyly and pes talovalgus are not. The association of miscarriage with multiple malformations is not surprising because this heterogeneous category probably

Table 2. Independent variables classified by group.

Group	Previous pregnancy* M (%)	SB (%)	Parental consanguinity (%)	First trimester illness Acute (%)	Chronic (%)	Previous infertility (%)	Socioeconomic level† (%)	Maternal age (years) Mean	(SE)	Interval between pregnancies (weeks) Mean	(SE)
Malformed SB	15·2	3·8	4·72	24·6	6·4	8·8	51·2	29·5	(0·6)	36·5	(2·5)
Multimalformed	16·0	1·6	2·47	15·8	11·7	8·5	51·2	28·1	(0·1)	35·0	(0·5)
Down's syndrome	16·1	1·9	1·39	13·7	9·9	10.9	58·6	35·0	(0·2)	44·4	(0·9)
Anencephaly	12·7	2·7	1·81	20·4	11·8	8.7	51·7	27·3	(0·4)	33·9	(1·6)
Spina bifida	13·3	4·3	0·00	16·2	6·8	8·9	57·9	27·9	(0·4)	33·0	(1·7)
Cleft lip	12·4	2·1	1·46	16·8	7·9	7.4	57·3	27·5	(0·2)	31·0	(0·9)
Hypospadias	13·8	1·0	2·02	9·9	8·9	8·0	50·7	27·5	(0·3)	33·5	(1·3)
Polydactyly	12·6	2·0	2·47	11·7	8·5	5·2	52·6	26·7	(0·2)	31·1	(0·7)
Pes equinovarus	16·6	1·5	1·58	10·4	8·3	8·1	50·1	27·6	(0·2)	33·6	(0·8)
Pes talovalgus	13·5	0·4	2·20	13·3	8·9	9.0	52·3	26·8	(0·4)	35·2	(1·6)
Hip dislocation	14·7	1·6	1·34	10·3	7·1	7·5	47·6	28·2	(0·2)	36·7	(0·8)
Other single malformed	13·3	1·6	1·29	12·3	7·4	7.1	50·4	27·6	(0·1)	34·5	(0·3)
LBW-SGA	14·2	2·8	0·30	12·8	8·9	6.3	49·4	27·2	(0·3)	32·1	(1·1)
LBW-AGA	17·5	3·4	0·00	12·0	7·4	5·2	56·4	27·4	(0·4)	29·0	(1·5)
Controls	11·9	1·3	0·99	8·6	5·7	6.3	49·0	27·2	(0·1)	33·6	(0·1)

* M = miscarriage, SB = stillbirth.
† Lower than 4
For abbreviations see Table 1.

Table 3. Linear logistic regression. odds ratios and attributable fractions.

		Independent variables						Confounding variables†						
		Previous miscarriage			Previous stillbirth				Illness					
Group	*n*	OR	(95% CI)	AF	OR	(95% CI)	AF	PI	Acute	Chronic	Maternal age	Consanguinity	IBP	SEL
Malformed SB	136	1 2	(0 6 to 2 4)	2·53	2 5	(0 8 to 8 2)	2 28	—	3 2	1 9	4 3	—	—	—
Multimalformed	2395	1 4	(1 2 to 1 6)*	4 57	1 3	(0 9 to 1 8)	0 37	1 4	2 0	2 0	1·3	2 2	—	—
Down's syndrome	1214	1 3	(1 0 to 1 6)*	3 72	1 3	(0 8 to 2 3)	0 44	1 6	1 4	—	9 5	—	—	0 8
Anencephaly	276	1 2	(0·7 to 1 8)	2 12	2 5	(1·1 to 5 4)*	1 62	—	2 4	2 2	—	—	—	—
Spina bifida	200	1 0	(0 6 to 1 8)	0 00	2·7	(1·2 to 6 3)*	2 71	—	2 0	—	—	—	—	—
Cleft lip	591	1 2	(0 9 to 1 6)	2 07	1 3	(0 6 to 2 6)	0 48	—	2 2	—	—	—	—	0 7
Hypospadias	375	0·9	(0 6 to 1·3)	1 53	1 0	(0 4 to 2 6)	0 00	—	—	—	—	—	—	—
Polydactyly	1008	1 0	(0 8 to 1·3)	0 00	1 3	(0 8 to 2 2)	0 46	—	1 5	1 4	—	2 5	—	—
Pes equinovarus	856	1 8	(1 4 to 2·2)*	7 38	1·1	(0 6 to 2 1)	0 14	—	—	1 6	—	—	—	—
Pes talovalgus	197	1 2	(0 7 to 2 0)	2 25	0 4	(0 1 to 3 0)	0 60	—	—	—	—	—	—	—
Hip dislocation	1103	1 4	(1 2 to 1 8)*	4 20	1 2	(0 7 to 2 1)	0·27	—	—	—	1·3	—	1 2	—
Other single malformed	9350	1 1	(1 0 to 1 3)*	1 21	1·1	(0 9 to 1 5)	0 15	—	1 5	1 2	—	—	—	—
LBW-SGA	598	1 3	(1 0 to 1 8)	3 28	2 0	(1 1 to 3 6)*	1 40	—	1 5	1 7	—	—	—	—
LBW-AGA	432	1 5	(1 1 to 2 1)*	5 83	2 8	(1 5 to 5 4)*	2 19	—	1 5	—	—	—	—	0 8

* *P*<0 05

† Results show only those odds ratios with *P*<0 01.

Abbreviations OR = odds ratio, AF = attributable fraction, PI = previous infertility, IBP = interval between pregnancies, SEL = socioeconomic level

includes many polygenic syndromes and associated severe malformations. The heterogeneity of the group prevents meaningful interpretation of associations between multiple malformed and miscarriage. Nevertheless, there is a suggestion that previous prenatal death and subsequent unfavourable outcomes are actually associated.

There is evidence that the risk of a neural tube anomaly is increased when there has been a previous miscarriage (Cuckle 1983). In the present study, only a weak association with stillbirth could be demonstrated. It is possible that different definitions for miscarriage and stillbirth, as well as unknown factors that differ geographically, could account for this apparent discrepancy.

The association of Down's syndrome with previous miscarriage in young mothers (Hook & Cross 1983) and of an increased rate of previous miscarriage in older mothers has been described (Risch *et al.* 1988). Our results showed a weak association between Down's syndrome and previous miscarriage and a strong association with maternal age. Nevertheless, the interaction between the independent and the confounding variable was not significant. This could be due either to the compensating effect of phenomena with opposing tendencies or to a true association. Heterogeneity could explain the positive association of the other malformed and Down's syndrome groups with previous miscarriage, with previous infertility or with chronic or acute disease.

To the authors' knowledge, the association of previous miscarriage with congenital dislocation of the hip and pes equi-

Table 4. Confounding variables and result of previous pregnancy for cases with significant odds ratio.

				Illness					
Group	RPP	*n*	PI (%)	Acute (%)	Chronic (%)	MMA	Consanguinity (%)	IBP	SEL (%)
Multimalformed	LB	1967	9 4	15 4	11·0	28 0	2 4	37 1	51 3
	M	392	9 5	17 5	12 6	28·3	2 3	19 5	51 1
Down's syndrome	LB	993	9 6	13 7	8 9	34 8	1·5	46 5	58 8
	M	199	15 7	13 7	14 8	35 5	0 5	26 6	58 4
Anencephaly	LB	234	7 3	19 8	11 3	27 4	2 3	36 2	51 8
	SB	8	25 0	0 0	12 5	27 1	0 0	18 7	50 1
Spina bifida	LB	165	8.7	14 8	6 8	27 8	0 0	34·2	58 0
	SB	9	12.5	11·1	22 2	31 4	0 0	23 4	57 1
Pes equinovarus	LB	714	7 9	9 9	7 4	27 5	1 7	35 4	50 0
	M	130	8 8	12 0	12 0	27 8	1 1	23 3	50 3
Hip dislocation	LB	920	7 0	9 6	7 1	28 1	1 1	38 8	47 7
	M	166	9 9	13 4	6 7	28 1	2 4	20·8	47 3
Other single malformed	LB	7935	6 3	11·6	6 6	27 5	1 2	36 1	50 3
	M	1265	11 3	15 8	10 8	28 0	1·1	20 6	50·7
LBW-SGA	LB	484	5 5	12 2	8 3	27 0	0 0	34 2	49 5
	SB	95	5 0	15 0	20 0	26 8	0 0	21 8	49 3
LBW-AGA	LB	356	4 8	12·2	8 3	27 1	0 0	34 6	56 5
	SB	10	0 0	9 4	12 5	29 3	0 0	32 9	56·1
	M	66	8 9	12 3	3·5	28 1	0 0	16 0	56 2

Abbreviations RPP = result of previous pregnancy; LB = livebirth, SB = stillbirth, M = miscarriage, PI = previous infertility, MMA = mean maternal age in years; IBP = mean interval between pregnancies in weeks.

novarus has never been described. Both traits can be considered deformities rather than true malformations and have little effect on long term survival.

Nevertheless, in both cases the association with previous miscarriage was strong. Each group was subdivided to investigate whether heterogeneity could explain the association, but heterogeneity was excluded. This could suggest that environmental rather than genetic factors may play a major role in the phenomenon.

In all groups, odds ratios were of similar magnitude for the risk factors as for the confounding variables, except for the cases for maternal age in Down's syndrome, and for consanguinity for malformed stillbirths.

Our results suggest that miscarriages and stillbirths in a previous pregnancy are factors that should be taken into account when the risk of malformations or low birthweight in a future pregnancy are assessed.

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FETAL AND NEONATAL MEDICINE

Lack of relation between fetal blood gases and fetal blood flow velocity waveform indices found in rhesus isoimmunised pregnancies

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ABSTRACT

Objective To investigate the relation between umbilical vein blood gas components and the vascular resistance in four fetal arteries in Rh-immunised pregnancies.
Design A prospective observational study over a 4-month period.
Setting King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.
Subjects Fifteen Rh-isoimmunised pregnant women.
Interventions Pulsed Doppler examinations of the embilical artery, fetal internal carotid artery, thoracic aorta and abdominal aorta before transabdominal fetal blood sampling from the umbilical vein on 38 occasions.
Main outcome measures Doppler flow velocity pulsatility index (PI), systolic/diastolic ratio (A/B) and resistance index (RI) in the four fetal arteries investigated were related to the umbilical vein blood gases and acid-base status (PO_2, PCO_2, O_2-content, CO_2-content, HCO_3, base excess and lactate concentration).
Results There were no correlations between the Doppler indices in any of the vessels studied and the blood gases components in the umbilical vein. The ratios between the corresponding Doppler indices in the different vessels were also independent of the blood gases and acid-base status and there were no significant differences in the Doppler indices in the same vessel between fetuses with blood gas values over the 75th centile and those with values below the 25th centile.
Conclusion This study does not support a reduction in peripheral vascular resistance in the fetal cerebrum in relation to fetal hypoxia in Rh-immunized pregnancies.

Several studies have shown an increased resistance in the placental circulation in growth-retarded fetuses, as judged by the A/B ratio of the Doppler flow velocity waveforms from the umbilical artery (Trudinger *et al.* 1985). The increased peripheral resistance in the placenta in growth retarded fetuses is accompanied by a reduction in the vascular resistance in the fetal cerebral circulation, suggesting a compensatory increase in the blood flow to the fetal brain (Wladimiroff *et al.* 1986). Such a brain-sparing effect in the growth-retarded fetuses correlates closely with fetal hypoxaemia (Vyas *et al.* 1990). We studied the relation between blood gases and vascular resistance in fetuses affected by rhesus isoimmunization to assess whether this redistribution of fetal blood flow also occurred when the hypoxaemia was caused by fetal anaemia.

Subjects and methods

Fifteen Rh-isoimmunized pregnant women underwent 38 transabdominal fetal blood samplings from the umbilical vein. On ten occasions in four women the fetus was hydropic at the time of the blood sampling. In 25 instances blood sampling was followed by fetal blood transfusion. Intramuscular premedication with 75 mg of meperidine (Demerol) and 25 mg promethazine (Phenergan) was given to the woman 30 min before the investigations. The umbilical vein was punctured free hand under ultrasound guidance. Blood gases (PO_2, PCO_2, O_2-content, CO_2-content, HCO_3 and base excess) were analysed on blood samples aspirated into heparinized syringes that were kept on ice until processed by a Corning 178 pH blood gas analyser (Corning Medical, Medfield, MA, USA) at 38°C with standard electrodes. Specimens for analysis of lactate were drawn into test tubes prepared with sodium fluoride and potassium oxalate and kept on ice until processed. Lactate was measured by an enzymatic spectrophotometric method (Marbach & Weil 1967) using an automatic analyser (ACA IV, Du Pont, F1).

Doppler examination of the fetal arteries was done immediately before the invasive procedure using an Acuson 128 Computed Sonography scanner (Acuson Corp. Moun-

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Table 1. Gestational age, haemoglobin, haematocrit, blood gases and lactate in the umbilical vein*.

	Mean	Median	Range	Normal values* Mean (SD)
Gestational age (weeks)	28·4	28	21 – 35	–
Haemoglobin (g/l)	76·4	81	9 – 140	124 (48)
Haematocrit (%)	0·23	0·24	0·2 – 0·42	0·38 (0·014)
pH	7·37	7·38	7·09 – 7·43	7·36 (0·08)
PCO_2 (kPa)	5·02	5·05	2·4 – 7·18	4·92 (1·06)
CO_2 content (mmol/l)	22·7	23·4	0·8 – 27·5	–
PO_2 (kPa)	5·4	5·3	2·5 – 8·5	7·32 (1·86)
O_2 content (mmol/l)	8·1	8·6	1·6 – 13·2	–
Lactate (mmol/l)	1·7	1·1	0·5 – 7·4	1·10 (0·50)
Base excess (mmol/l)	–2·4	–2·1	–15·2 – 2·0	–4·2 (4·6)
HCO_3 (mmol/l)	21·9	22·0	11·1 – 26·2	20 (4·6)

* Normal values from midtrimester pregnancies (Forestier *et al.* 1986; Soothill *et al.* 1986) are used as reference.

tain View, CA, USA). A 3 MHz real-time transducer with a built-in pulsed Doppler transducer (S 328) was used. The output power (SPTA) was kept at the lowest setting (50 mW/cm^2), and the high-pass filter was set to 100 Hz. The sample volume (gate) was placed over the relevant vessel and the pulsatility index (PI) (Gosling *et al.* 1971), the systolic/diastolic ratio (A/B) (Stuart *et al.* 1980), the resistance index (RI) (Pourcelot 1974) and the pulse rate were calculated as the mean over five consecutive cardiac cycles. All measurements were conducted during fetal quiescence. The Doppler examinations of the fetal descending thoracic aorta was performed just above the diaphragm; the abdominal aorta was studied just cranially to the bifurcation; the internal carotid artery was studied close to the entrance of the vessel into the circle of Willis. The carotid artery could not be identified with certainty on four occasions which leaves only 34 examinations from this artery. The examinations of the umbilical arteries were carried out where the cord was easily accessible and the Doppler signal of the highest quality. The indices from the umbilical arteries were normalized for gestational age by dividing our results by reference values for the appropriate gestational age (Gerson *et al.* 1987). Waveform indices were studied both corrected and uncorrected for gestational age. The indices from the other vessels were used as measured since these indices are independent of the gestational age represented in our study.

Statistics

The results were analysed using the Statgraphics statistical software version 3 (STSC, Inc, 2115 East Jefferson Street, Rockville, MD, USA). As the results were not normally distributed, non parametric methods were used. Medians and ranges are given unless otherwise indicated. The Wilcoxon signed rank test was used for comparisons of indices from different vessels. Correlation between the variables was examined by Kendall's rank correlation (traditional correlation, least sum of squares. has also been tested and gave the same results). A P value $<0·05$ was considered as statistically significant.

Results

The haemoglobin, haematocrit and blood gas values are given in Table 1. Our results come from a wide spectrum of normal, severely anaemic, acidotic and hypoxaemic fetuses. The Doppler indices from the different fetal vessels are shown in Table 2. The Doppler indices from the hydropic fetuses were not significantly different from the indices in the other fetuses.

There were significant correlations between concentrations of haemoglobin and lactate ($r = -0·54$, $P<0·0001$), bicarbonate ($r = 0·49$, $P<0·003$), CO_2 content ($r = 0·47$, $P<0·004$), and base excess ($r = 0·32$, $P<0·003$). A close negative correlation was also found between oxygen content and lactate ($r = -0·37$, $P<0·003$), but the relations between haemoglobin and PO_2, pH and PCO_2 were not significant as was the relation between PO_2 and O_2 content.

There were no significant correlations between the Doppler indices in any of the fetal vessels studied and umbilical

Table 2. Doppler indices from the umbilical artery, thoracic, aorta abdominal aorta and internal carotid artery.

		A/B ratio	PI	RI
Vessel	(n)	Median (range)	Median (range)	Median (range
Umbilical artery				
Uncorrected	38	3·05 (2·59–11·10)	1·19 (0·92–2·24)	0·72 (0·61–0·90)
Corrected	38	1·04 (0·66– 2·78)	1·05 (0·76–1·79)	1·01 (0·81–1·20)
Thoracic aorta	38	8·53 (4·81–18·69)	2·17 (1·35–2·81)	0·88 (0·79–0·95)
Abdominal aorta	38	4·70 (3·08–11·80)	1·47 (1·09–2·22)	0·79 (0·68–0·91)
Internal carotid artery	34	6·54 (2·50–17·28)	1·64 (0·90–2·30)	0·83 (0·60–0·91)

PI = pulsatility index, RI = resistance index.

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FETAL AND NEONATAL MEDICINE

A comparison between computerised (mean range) and clinical visual cardiotocographic assessment

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ABSTRACT

Objective To compare computer cardiotocographic (CTG) analysis with clinical visual analysis.
Design A retrospective blind comparison of the two techniques of CTG assessment.
Setting Fetal Assessment Unit, King's College Hospital, London.
Subjects One hundred CTG traces of women referred to the unit were studied; the traces were taken after 32 weeks' gestation, within 10 days of delivery and where outcome was known.
Interventions The CTG traces were assessed both by the computer (System 8000 computerised CTG analyser, Oxford Sonicaid Ltd) and visually, by one of us.
Main outcome Computer mean range from 0 to 80 in ms clinical visual CTG score from 0 to 80 (arbitrary units). A score <20 is ominous; suspicious when between 20 and 30; and normal when >30.
Results There was close correlation between the computer mean range and clinical visual assessment ($r = 0{\cdot}78$, $n = 100$, $P = 0{\cdot}001$). However, there were 13 occasions where the computer classified the trace as abnormal when clinical visual assessment was normal, indicating computer false positives. All these pregnancies had normal outcomes. There were no traces where computer analysis was normal and clinical visual assessment abnormal.
Conclusions Computerised CTG analysis gives an objective assessment which agrees closely with experienced visual assessment. It also provides a number which can be used to assess the value of fetal heart rate analysis.

Kennedy (1833) suggested there was an association between audible abnormality of the fetal heart rate pattern and risk to the fetus. The development of technology permitting the continuous electronic monitoring of the fetal heart rate led to the introduction of antepartum cardiotocography (CTG) by Hammacher (1966). Antenatal CTG now plays a primary role in fetal surveillance in many British hospitals (Wheble *et al.* 1989). Assessment of the effect of this on perinatal outcome has been difficult. The need to assess the CTG in the context of the clinical situation is important (Flynn *et al.* 1982). Intra- and inter-observer variability (Lotgering *et al.* 1982; Nielsen 1987) has highlighted the need to define assessable features such as reactivity (Flynn *et al.* 1982) or to consider scoring systems (Trimbos & Keirse 1978). Electronically derived indices, which focus on electronic events rather than the whole compound trace, may have disadvantages (Escarcena *et al.* 1979), but such indices may assist screening by less experienced staff. Computer systems have been developed that are capable of objective assessment. The potential advantages of such systems include consistent numerical analysis and archiving, thereby facilitating audit and research.

An easy to use reliable system of computer CTG analysis is now commercially available and was compared with clinical visual assessment to assess its potential role.

Subjects and methods

CTG traces from 100 pregnant women who had been referred to the Fetal Assessment Unit at King's College Hospital were studied retrospectively; the characteristics of the pregnancies and the practices of the Unit have been described previously (Soothill *et al.* 1991). The pregnancies were selected to include a wide range of CTG patterns that had been recorded after 32 weeks' gestation and within 10 days of delivery and for which the outcome was known.

Fetal heart rate patterns and uterine contractions were recorded with a Doppler ultrasound CTG machine (Sonicaid FM7, Oxfod Sonicaid Ltd, Chichester). The woman recorded fetal movements by pressing a button which marked the CTG trace. Each trace was at least 20 min long. Simultaneous computerised analysis of the trace was done with the System 8000 computerised CTG analyser (Oxford Sonicaid Ltd, Chich-

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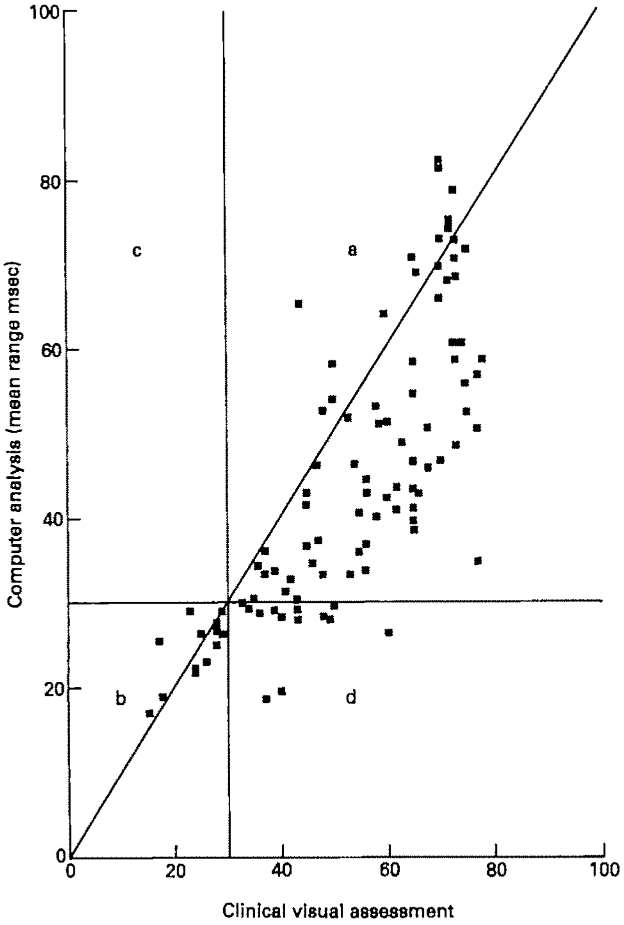


Fig. 1. Comparison of computer CTG analysis (mean range in ms) with clinical visual assessment.

ester). Although it records many variables from the CTG trace, it measures the fetal heart rate variation by averaging the one-minute range of pulse intervals about the baseline and records the result as the mean range in milliseconds (ms) (Dawes *et al.* 1985). A mean range value of 30 ms was taken as the lower limit of normality.

The Sonicaid FM7 CTG traces were assessed visually by one of us (D.M.F.G.) who did not know the woman's name, clinical details (including gestational age) or the computer analysis. The assessor was asked not to duplicate the mean range visually, instead the CTG was assessed according to the principles of interpretation in clinical practice (Gibb & Arulkumaran 1992) and standards agreed by the International Federation of Obstetrics and Gynaecology (FIGO 1987) and then scored on a scale of 0–80 to give an indication of clinical concern. The scale was set for comparison with the mean range, so that a score of less than 20 indicated an ominous pattern (normally requiring immediate delivery); a score between 20 and 30 indicated a suspicious pattern (requiring closer monitoring and correlation with the clinical situation). A score of 30 or more indicates good fetal health. The presence of fetal movements, a normal baseline rate, accelerations, normal variability and the absence of decelerations indicate a healthy autonomic nervous system. The clinical visual score given was a sliding scale taking into account all these features; if all were optimal in the presence of contractions then a score of more than 70 was given. The score was reduced to 60 plus if there were no contractions. If movements were limited and there were fewer than six accelerations, the score would be in the 50s. If there were only two accelerations and the baseline variability was less than 10, the score would be less than 50. The absence of accelerations was the criterion for a score of less than 30 (suspicious). More than two suspicious features led to a score of less than 20 (abnormal). The above should be viewed not as a rigid framework but as a showing how a composite assessment of all these features resulted in the final score, which could be any number up to 80.

Pearson's correlation coefficient was used to compare the results statistically. Although Pearson's coefficient is an adequate comparison of the relation between the two, this can be misleading as an assessment of the differences between the tests. We therefore also assessed the data using a graphical presentation of the difference between the tests for each woman plotted against their mean (Bland & Altman 1986).

Results

The results of the computer and visual assessments of the 100 CTGs are shown in Fig. 1. Lines indicating the limits of normality divide Fig. 1 into four sectors labelled a, b, c and d. Points in sectors a and b indicate agreement between computer analysis and visual clinical assessment; points in sector a indicate that both were normal (n=74), whereas those in sector b (n=13) indicate that both were abnormal. Points in sectors c and d indicate disagreement between computer analysis and visual clinical assessment. On 13 occasions, the computer classified the trace as abnormal when the clinical visual analysis was normal (sector d). There were no occasions where the computer analysis was normal and the clinical visual assessment abnormal (sector c). The outcome of the 13 pregnancies in sector d were all normal with respect to Apgar scores, cord pH, admission to SCBU and caesarean section; so these abnormal computer analysis results could be considered false positives.

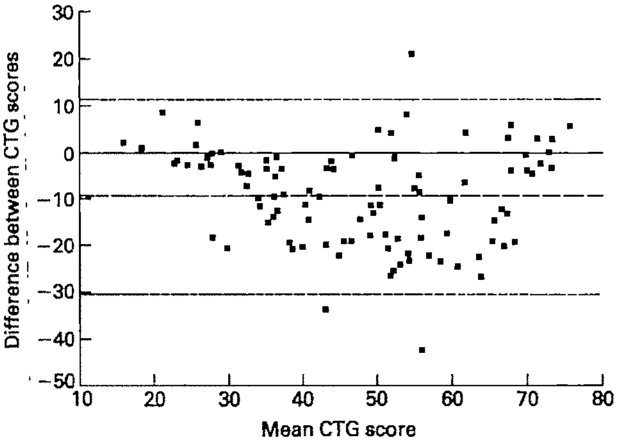
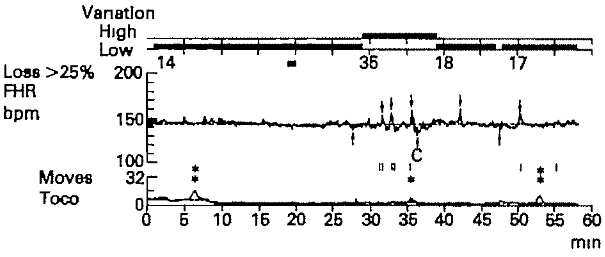


Fig. 2. A visual representation of the difference between the two tests (see text). Lines indicate the mean (dashed line) ±2 SD (dotted line) for the limits of agreement.



Dawes/Redman criteria WERE NOT met at 58 min

Normal values

Analysis at 58 min.

```
(0)     1. Signal loss (%)................. ........... 1·4
        2. Contraction peaks............. ............. 3
(>12)   3. Fetal movements (per h).......... .........7       *
               per min in high 0·50 in low 0·04
(<160)  4. Basal heart rate (bpm)...................144
(>8/h)  5. Accelerations >10 bpm & 15 s......... .. 5
                          >15 bpm & 15 s............ 2
(0)     6. Decelerations    Total..................... 3     C
                           <10 bpm................ 2
                           >20 lost beats.......... 0
(>4)    7. High episodes (min): Threshold 24 ms.10
           Low episodes (min)......................... 46
        8. Variation over all (Mean range: ms). 19·6     **
                           (Mean range: bpm).7·1
           Short term variation (ms).................4·0
           Interpretation of variation  Normal       >30 ms
                                        Questionable 20–30 ms
                                        Abnormal     <20 ms
However, note high episodes of 10 min with 0·50 moves/min.
```

Fig. 3. A computer CTG analysis showing reduced heart rate variability as a result of a fetal sleep state. The clinical visual assessment was normal (40) and the outcome was normal.

There was a reasonable correlation between the computer mean range and clinical visual assessment (r=0·78, n = 100, P = 0·001). The line of equality was plotted on the figure through the points (100, 100) and the origin and this showed that the computer tended to give lower values. This difference between the two tests is shown in Fig. 2 by plotting the difference between the tests on each woman against the mean for each patient.

Discussion

There was a strong correlation beween the two methods of analysis. Although the numbers were small, disagreement between computer analysis and clinical visual assessment occurred in one direction only (computer false positives). These traces had segments of reduced variability with no accelerations followed by reactivity suggesting a period of fetal sleep and Fig. 3 shows the computer analysis of the CTG from one of these pregnancies. The computer mean range was 19·6 ms whereas the clinical visual assessment was normal (40). The first half of the trace corresponds to a fetal sleep pattern which is followed by a period of normal variability with a number of accelerations but the total fetal heart variability was still low. This illustrates, as stressed by the computer software, that the mean range should be used to indicate the need for experienced clinical review and not be used as a diagnosis of fetal hypoxia. For every two traces that the computer highlights for clinical review, there will be one where clinical review identifies a false posititve.

There have been criticisms of the application of the CTG in clinical management before it was fully assessed. Lumley *et al.* (1983) and Kidd *et al.* (1985) failed to demonstrate a beneficial effect on fetal outcome while others believe that intervention on the basis of specific CTG abnormalities prevents poor fetal outcome (Beischer *et al.* 1983; Chew *et al.* 1985). Major problems with these studies have been the subjectivity of CTG analysis, lack of prospectively agreed criteria for analysis and the need to incorporate the whole clinical picture. Visual scoring systems have attempted to quantify CTG changes (Hammacher *et al.* 1974; Fischer *et al.* 1976; Meyer-Menk *et al.* 1976; Pearson & Weaver, 1978; Lyons *et al.* 1979; Varma 1984) but these still have the problems of subjectivity and divide continuous pathophysiological variables into artificial groups. Computerised analysis provides an objective and reproducible assessment of the CTG and will help research into the value of fetal heart rate analysis. For example, recent publications have reported that the mean range predicts fetal blood gases at cordocentesis (Ribbert *et al.*, 1991); another study compared computer CTG analysis with fetal blood velocity studies (Hofmeyr *et al.* 1991) and it has been used to assess the value of fetal heart monitoring in antenatal complications (Ajayi *et al.* 1992).

Our findings show that computer analysis can provide an assessment that is similar to that of an experienced obstetrician. This suggests that computer analysis could be used in management protocols to indicate when review by senior medical staff is required (e.g., when the mean range is below 30 ms). A mean range of 30 ms or more is reassuring and on no occasion in this series was the computer classification of a normal CTG changed by expert clinical visual assessment. Computer analysis can therefore allow more efficient use of senior medical staff and reduce the time pregnant women spend waiting in a fetal assessment unit, however, efforts must continue in the education of all those involved in CTG analysis.

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GYNAECOLOGY

The risk of acute myocardial infarction after oestrogen and oestrogen–progestogen replacement

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ABSTRACT

Objective To determine the relative risk of developing a first acute myocardial infarction after treatment with oestrogens alone or oestrogen–progestogen combinations.

Design Prospective cohort study utilizing a prescription-based and record linkage system for a follow-up period from 1977 to 1983. Average individual observation time was 5·8 years.

Setting The entire female population of the Uppsala Health Care Region (1·4 million inhabitants), one-sixth of the total Swedish population

Subjects 23 174 women aged 35 years and older, identified from pharmacy records as having been prescribed non-contraceptive oestrogens during 1977–1980.

Outcomes Admissions to hospitals for first acute myocardial infarctions.

Results Overall, 227 cases of a first acute myocardial infarction were observed as against 281·1 expected, RR=0·81 (95% confidence limits 0 71 to 0·92). Women who were younger than 60 years at entry into the study and prescribed oestradiol compounds (1–2 mg) or conjugated oestrogens (0·625–1·25 mg) showed a significant 30% reduction of the relative risk (RR=0·69, 0·54 to 0·86). Those prescribed a combined oestradiol-levonorgestrel brand also demonstrated a significantly lowered relative risk (RR=0·53, 0·30 to 0·87). The risk estimates were near unity during the first year of follow-up but decreased during subsequent years. Exposure to the weak oestrogen oestriol did not alter the risk.

Conclusion Hormonal replacement therapy with oestrogens alone, and maybe also when cyclically combined with progestogens, can reduce the risk of acute myocardial infarction.

The use of replacement oestrogens, either alone or opposed by cyclically added progestins, has increased since the 1960s and is currently popular in most western countries including Scandinavia (Hemminki 1988; Persson *et al* 1983a). The benefits of such therapy include efficient relief of vasomotor symptoms and urogenital discomfort and the reduction of postmenopausal osteoporosis and associated hip fractures (Cummings *et al.* 1985; Naessén *et al.* 1990). Increased risks of endometrial cancer after unopposed oestrogen exposure (Persson *et al.* 1989) and possibly of breast cancer after long-term treatment (Bergkvist *et al.* 1989) have been recognized. Because coronary heart disease becomes the most frequent cause of death in women after menopause (Johansson *et al* 1983), any effect on the risk of coronary heart disease in treated women would have important implications.

The association between unopposed oestrogen replacement and coronary heart disease has been investigated in numerous epidemiological studies. Reviews of data (Stampfer *et al.* 1991; Barrett-Connor & Bush 1991) revealed no association in some but a reduced risk in most case-control and prospective studies (Stampfer *et al.* 1985; Bush *et al.* 1987; Petitti *et al.* 1987; Henderson *et al.* 1988a; Criqui *et al.* 1988; Avila *et al.* 1990; Wolf *et al.* 1991). A few studies have shown an increased risk of cardiovascular disease (Jick *et al.* 1978; Wilson *et al.* 1985). In spite of contradictory results, and although the validity of observational data has been questioned, a substantial protective effect from oestrogen replacement is widely believed to exist (Stampfer & Colditz 1991; Barrett-Connor & Bush 1991).

The addition of progestogens is commonly recommended to protect the endometrium from development of hyperplasia and neoplasia (Whitehead & Lobo 1988). There is concern that such combined regimens may reduce or eliminate cardioprotection (Henderson *et al.* 1988b). Oestrogens alone produce favourable lipoprotein patterns (Bush & Barrett-Connor 1985; L'Hermite 1990) which may be reversed by added progestogens (Hirvonen *et al.* 1981). Three previous studies of combined treatments (Nachtigall *et al.* 1979; Thompson *et al.* 1989; Hunt *et al.* 1990) have provided data that were insufficient to allow final conclusions on the effect of added progestogens.

In the present population-based prospective cohort study

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of 23 000 women we have explored the risk of myocardial infarction in relation to replacement therapy, both with oestrogens alone and when combined with progestogens.

Subjects and methods

Cohort and subcohort

From April 1977 through March 1980, prescription forms for non-contraceptive oestrogens were notified to us by all pharmacies within the entire Uppsala health care region, comprising six counties and one-sixth of the total female population of Sweden. The 77 000 prescription forms notified constituted an estimated 92% of all such prescriptions issued to women in this region. Only one of the brands consisted of tablets in which oestrogen and progestogen were combined in the same tablet. The national registration number (a 10-digit number that enables exclusive identification of the individual and which allows follow-up through record linkage), data on the brand, dosage, and treatment schedule and purchase date were computerized. These prescription data related to a final cohort of 23 247 women, 35 years of age or older who lived in the Uppsala health care region and had filled at least one prescription for an oestrogen-containing preparation (Persson *et al.* 1983b).

The prescription data permitted characterization of exposure to oestrogenic drugs for all women in the cohort during 1977–1980 However, hormone use before and after the three-year recording period could not be ascertained and intake compliance for the prescribed drug was not known

The total cohort was characterized only from the prescriptions they had been issued during the three years of the study. To further characterize the cohort with regard to lifetime hormone exposure and the prevalence of certain risk factors for coronary heart disease, a random sample (subcohort) of 735 women from the total cohort was surveyed in 1980 and 1984 by means of a postal questionnaire, as previously described (Persson *et al.* 1983; Bergkvist *et al.* 1989a). Nine per cent had not taken the prescribed drug, 50% started treatment before 1977, the median duration of oestrogen use was approximately 3·5 years and 21% of the women in the subcohort were continuing these treatments at the end of 1983. The use of various oestrogens and progestogens is shown in Table 1.

Exposure categories

Three different exposure categories were defined (not mutually exclusive) on the basis of prescription records The subcohort was used to assess concordance between categories defined from prescriptions and from questionnaire data, respectively.

1. Women prescribed various hormonal compounds, three groups

(a) Women ever prescribed a specific oestrogen–progestogen combined brand.

A total of 5654 women had been prescribed this brand, containing 2 mg of oestradiol valerate for 21 days and 250 μg of the progestogen levonorgestrel for 10 days at the end of the cycle. According to the questionnaire data, 41% of all the women prescribed oestradiol compounds or conjugated oestrogens were ever exposed to progestogens. Women on this specific brand represented 81% of all those women who had ever received progestogen-combined regimens.

(b) Women ever prescribed other oestradiol or conjugated oestrogen brands.

Altogether 11 545 women were prescribed oestradiol compounds or conjugated oestrogens in dosages of 1 and 2 mg, and 0·625 mg and 1·25 mg, respectively. Among these, 11% were estimated to have ever received progestogen combined therapy.

Oestradiol and conjugated oestrogens are considered to be relatively potent They are equally efficient at the usual dosages to treat vasomotor symptoms and result in similar plasma concentrations of oestradiol and oestrone (Von Schoultz 1988).

The questionnaire data from the subcohort suggest that 95% of the women in the complete cohort who had the oestradiol compound or conjugated oestrogen group prescibed actually used these potent oestrogens.

(c) Women prescribed other oestrogens only.

Other oestrogens, chiefly oestriol compounds, are biologically weak oestrogens and are usually given in daily doses of 1 mg to women of more advanced age to treat symptoms associated with urogenital atrophy (Persson *et al.* 1983a). These compounds were prescibed for 5975 of the main cohort; in the subcohort, 81% of the women reported using oestriol only.

2. Women aged <60 compared with >60 years at time of the first notified prescription

Nearly 82% of the cohort women were less than 60 years of age at time of the first notified prescription and the questionnaire data suggest that 84% of these had ever used potent oestrogens (oestradiol compounds or conjugated oestrogens). In older women, 53% had ingested only the less potent compounds (mainly oestriol compounds). Approximately 40% of these older women had started their treatment before cohort entry.

Table 1. Use of various oestrogens and progestogens, as reported by women in a questionnaire from the subcohort (a random sample of 653 women).

A. Proportions (%) of treatments with specified oestrogens		
Oral		
Oestradiol valerate	1–2 mg	51%
Ethinyl oestradiol	5–10 μg	5%
Conjugated equine oestrogens	0·625–1·25 mg	22%
Mixed oral/parenteral		
Other oestrogens (83% of this group used oral oestriol ≤ 1 mg, 3% had parenteral treatment)		22%
B Proportions (%) of combined treatments— 31% of all—with specified progestogens		
Levonorgestrel	250 μg	65%
Medroxyprogesterone acetate	5–10 mg	18%
Norethisterone acetate	5–10 mg	15%
Lynestrenol	5 mg	2%

3. Women with early vs *late recruitment periods*

About half of the women who had their first prescription notified before July 1978 were current takers at the time of recruitment. Those whose first prescription was notified later had newly started treatment, since a prescription form is valid only for one year from the date of issue. The questionnaire data suggest that treatment duration tended to be longer in the former group, a mean of 5 years, as compared with 3 years in the latter group.

Follow-up

To ascertain all instances of a first acute myocardial infarction in the cohort, we linked cohort members through their national registration number to a registry including data on hospital admissions—the Inpatient Registry. This registry contains information on all episodes of inpatient care for somatic conditions within the Uppsala health care region since 1965, including date of admission and numerical codes for diagnoses. Coverage of admissions was almost complete (97%) (Naessén *et al.* 1989). The first episode of acute myocardial infarction was defined by the ICD-8 codes 410,00 (acute myocardial infarction with hypertension) or 410,99 (acute myocardial infarction, hypertension not indicated), occurring after entry into the cohort, i.e., the purchase date of the first prescription.

Observation of the outcome started at the date of the first recorded prescription and continued until the end of the study period (31 December 1983) or the date of death, emigration, or admission because of a first acute myocardial infarction (Table 2). The number of expected cases was calculated by multiplying the person-years (a total of 133 372 in the cohort) by the average incidence rates of acute myocardial infarction, in five-year age groups, among the total female population in the Uppsala health care region. These incidence rates were based on 8162 cases of a first acute myocardial infarction and 2 179 174 person-years in the time period. Since the number of person-years in the cohort was small compared to that in the background female population (6%), the cohort was not excluded before calculating the expeded incidence rates.

Statistical methods

The observed number of women with a first acute myocardial infarction was compared with that expected, to produce estimates of relative risk (RR) (i.e., standardized incidence ratios) (Kleinbaum 1982). The 95% confidence limits (CL) were calculated on the assumption that the observed cases had a Poisson distribution.

In order to judge the effect on the risk of myocardial infarction, relative to that of the background population, of different exposure variables after adjustment for the effect of other variables, multivariate analyses were performed. We used Poisson regression analyses, in which the exposure variables were assumed to act multiplicatively on the age-specific rates in the background population. Estimates were obtained on the basis of grouped yearly data using the maximum likelihood method by means of the GLIM (generalized linear model) system. The deviance was used as a measure of model fit (Breslow *et al.* 1983).

Results

From April 1977 to the end of 1983, 23 247 women entered the cohort; 73 were excluded since they had had an acute myocardial infarction previously, leaving 23 174 at risk of a first myocardial infarction. Altogether 876 women died and 26 emigrated during the observation period. The cohort members had a median age of 53·9 years at entry and contributed 133 372 person-years of observation (Table 2). The average observation time per individual was 5·8 years.

Univariate analyses

During the observation period, 227 women were admitted (alive on admission) with a first episode of acute myocardial infarction, as compared with an expected 281·1, yielding an overall relative risk estimate (RR) of 0·81 (95% confidence limits (CL) 0·71 to 0·92); for those ever prescribed oestradiol and/or conjugated oestrogens the relative risk was 0·74 (95% CL 0·61 to 0·88); and other oestrogens only, 0·90 (95% CL 0·74 to 1·08) (Table 3). The relative risks tended to decrease with increasing duration of follow-up from a level close to unity during the first year (RR = 0·96) to RR = 0·76 during the last (Table 3). In the subgroup of women ever prescribed the progestogen-combined brand, 16 myocardial infarctions were observed versus 32·28 expected, RR = 0·50 (95% CL 0·28 to 0·80) (Table 4).

Table 2. Distribution of women in the cohort at risk of a first acute myocardial infarction and accumulated person-years of observation, by age at entry. Number of cases of myocardial infarction during the follow-up period to the end of 1983.

Age at entry (years)	Age distribution (*n*)	No. of accumulated person-years	No. of acute myocardial infarctions
35–39	401	865·0	0
40–44	1382	3900·6	0
45–49	4925	15 383·0	6
50–54	7481	36 259·4	18
55–59	4752	38 605·9	41
60–64	1882	20 339·1	45
65–69	1124	8732·1	35
70–74	664	4976·4	34
75+	563	4310·4	48
Totals	23 174	133 371·9	227

Table 3. Observed and expected number of cases of acute myocardial infarction by year of follow-up. Relative risk estimates (RR) and 95% confidence limits (CL), over all and among women prescribed oestradiol or conjugated oestrogens (E2/CE) ever and other oestrogens (OE) only.

	E2/CE ever				OE only				Overall*			
Year	Obs	Exp	RR	CL	Obs	Exp	RR	CL	Obs	Exp	RR	CL
1977	5	5·69	0·88	(0·29, 2 05)	4	3·64	1·10	(0 30, 2·81)	9	9·33	0·96	(0·44, 1·83)
1978	9	15·83	0 57	(0·26, 1·08)	16	11·53	1 39	(0 79, 2·25)	25	27·36	0·91	(0 59, 1·35)
1979	18	20·88	0 86	(0·51, 1·36)	16	17·00	0 94	(0 54, 1·53)	34	37 88	0·90	(0 62, 1·25)
1980	18	24·69	0 73	(0·43, 1·15)	21	20·88	1 01	(0 62, 1·54)	39	45 57	0 86	(0 61, 1 17)
1981	21	27·47	0 76	(0 47, 1·17)	18	22·04	0·82	(0·48, 1·29)	39	49·51	0·79	(0·56, 1·08)
1982	24	30·48	0·79	(0·50, 1·17)	13	23·10	0 56	(0 30, 0 96)	37	53 58	0·69	(0·49, 0·95)
1983	22	33 65	0·65	(0·41, 0·99)	22	24·22	0 91	(0 57, 1 38)	44	57·87	0·76	(0·55, 1·02)
Whole period	117	158·69	0·74	(0·61, 0·88)	110	122 41	0·90	(0·74, 1 08)	227	281·10	0·81	(0 71, 0 92)

*The RR associated with each year was 0 95 (95% CL 0 88, 1·02), according to an analysis in continuous linear form.

Incidence rates of first myocardial infarctions among the cohort resembled those in the background population at ages 45–49 years, but were lower in older age groups, especially in those aged 55–59 years (Fig. 1).

Stratified analyses

The lowest relative risk in the whole group of women ever pre-scribed oestradiol compounds or conjugated oestrogens was for those younger than 60 years at cohort entry and who were recruited before July 1978 (RR = 0·67, 95% CL 0·51 to 0·86). For the entire period, these younger women showed a 31% lowered relative risk (RR = 0·69, 95% CL 0·54 to 0·86) (Table 4). In women prescribed the oestradiol–progestogen combined brand before age 60, significant risk reduction was observed (RR = 0·53, 95% CL 0·30 to 0·87), compared with those receiving oestradiol compounds or conjugated oestrogens without a fixed progestogen combination (RR = 0·74, 95% CL 0·56 to 0·96). Women prescribed other oestrogens only had risk estimates in all strata slightly below and not significantly different from unity (data not shown).

Multivariate analyses

The full multivariate model used to investigate the ratio between the observed and expected numbers of cases included as covariates follow-up years, compound groups (oestradiol or conjugated oestrogens ever *vs* other oestrogens only), age at entry, and period of entry. The fit of the model was excellent (deviance 49·09 with 47 df and follow-up years in continuous linear form). The risk declined, but not significantly, with increasing years of follow-up, the RR being 0·80 (95% CL 0·39 to 1·65) in the last year (1983) as compared with the first (1977); the RR associated with each year was 0·95 (95% CL 0·89 to 1·03). The relative risk of women prescribed oestradiol or conjugated compounds was 0·73 (95% CL 0·59 to 0·90) after adjustment for other prescription-based exposure variables. This risk was lower, but not significantly so, than for those prescribed other oestrogens (RR = 0·83, 95% CL 0·62 to 1·12), implying a RR for all follow-up years compared with the background population of 0·88 (95% CL 0·64 to 1·19) for those prescribed other oestrogens. Comparisons between age groups and recruitment periods

Table 4. Observed and expected numbers of cases of a first acute myocardial infarction, stratified by compound groups (potent oestrogens), age and period. Relative risk estimates (RR) and 95% confidence limits (CL).

		Compound groups									
		E2 + LNG* (fixed brand)				E2/CE† (except the fixed brand)				All E2/CE	
Period of entry	Age at entry	Obs	Exp	RR	CL	Obs	Exp	RR	CL	RR	CL
≤30/6–78	<60	6	22 18	0·27	(0·10, 0·59)	54	68·01	0·79	(0·60, 1·04)	0·67	(0 51, 0·86)
	≥60	1	3 59	0 28	(0 01, 1·55)	38	39·31	0·97	(0·68, 1·33)	0·91	(0·66, 1·24)
	All	7	25·77	0 27	(0 11, 0·56)	92	107 32	0·86	(0·69, 1 05)	0·74	(0·60, 0·91)
≥1/7–78	<60	9	6 14	1 47	(0 67, 2·78)	4	10 06	0 40	(0 1, 1·02)	0·80	(0·43, 1·37)
	≥60	0	0 37	—	—	5	9 05	0 55	(0 18, 1 29)	0·53	(0·17, 1·24)
	All	9	6·51	1 38	(0 63, 2 63)	9	19·11	0·47	(0 22, 0·89)	0·70	(0 42, 1·11)
Whole period	<60	15	28·32	0 53	(0·30, 0 87)	58	78·06	0·74	(0 56, 0·96)	0·69	(0·54, 0·86)
	≥60	1	3·96	0·25	(0·01, 1 41)	43	48·36	0·89	(0·64, 1·20)	0·84	(0·61, 1·13)
	All	16	32·28	0 50	(0·28, 0·80)	101	126·42	0·80	(0·65, 0·97)	0·74	(0·61, 0·88)

*E2: Oestradiol valerate 2 mg; LNG. levonorgestrel 250 µg 10/21 days.

†E2/CE: Oestradiol compounds (1–2 mg) or conjugated oestrogens (0 625–1 25 mg).

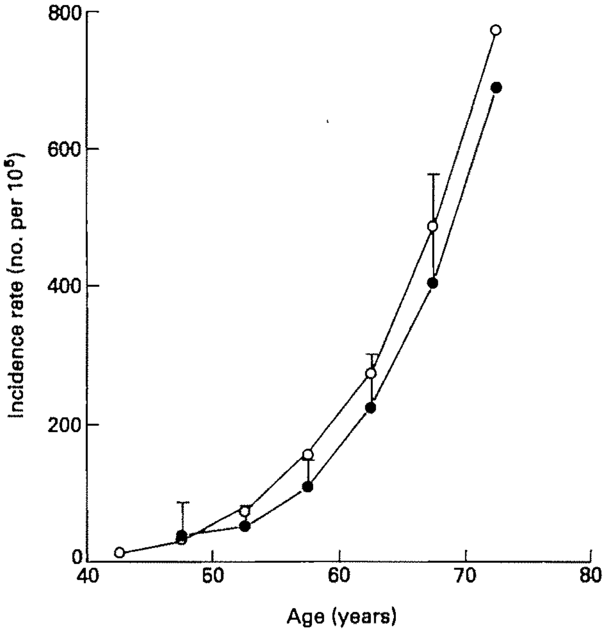

Fig. 1. Age-specific rates and 95% error bars for first acute myocardial infarctions among women in the cohort (closed circles) and background population (open circles), for all types of oestrogens.

did not reveal any apparent differences. No significant interaction effects were found.

Discussion

Women prescribed any type of non-contraceptive oestrogen had evidence of a reduced risk of a first acute myocardial infarction as compared with women in the general population. The protective effect was about 30% for women prescribed potent oestrogens such as oestradiol compounds or conjugated oestrogens at perimenopausal ages (Table 4). Those exposed to less potent oestrogens, mainly oestriol compounds, had no significant alteration of the risk (Table 3). Because the protective effect seemed to persist during the seven year follow-up period, during which many women had discontinued their treatment (Table 3), it may also persist after the termination of oestrogen use. In women prescribed 2 mg of oestradiol valerate combined with a high-dose and potent progestogen, levonorgestrel 250 μg for 10 days (Whitehead *et al.* 1981) there was also evidence of protection, with a 50% reduced relative risk. This indicates that the cyclical use of progestogens may not affect the protective effect exerted by potent oestrogens alone.

The present design has a number of methodological advantages. It was a population-based study with a sample large enough to have an 83% power to detect a 20% or greater protective effect on the risk of myocardial infarction ($\alpha = 0{\cdot}05$, one-sided test) and there was complete follow-up through record-linkage, a distinct end-point, the ability to study the effects of oestrogens with differing potencies and, perhaps most importantly, the risk associated with the use of oestrogens combined with progestogens.

On the other hand, the study has some important limitations. A key issue is whether the cohort women were at a lower risk from the start as compared with women in the background population. Women with risk factors for, or symptoms of, coronary heart disease, may have been excluded from hormonal treatment, a selective prescribing pattern that may confound results in observational studies (Vandenbroucke 1991).

The prevalence of some important factors relevant to the risk of myocardial infarction was compared between the cohort—as obtained from the subcohort sample questionnaire (Persson *et al.* 1983c)—and the underlying total female population (Table 5). A questionnaire similar to the one completed by the subcohort was administered in 1982 to an age-matched sample of 1325 women from the reference population, of whom 78% responded (Bergkvist *et al.* 1988). The cohort women did not differ from the reference women with respect to age at menarche and menopause or history of diabetes mellitus and hypertension. Cohort women were, however, comparatively more likely to have had an oophorectomy or a hysterectomy; to practise regular physical exercise; to be leaner; to be current smokers; and to have a somewhat higher level of education (Table 5). Since data on risk factors were not available for all cohort women, direct adjustment of the risk estimates could not be made in the analyses. In order to examine the potential confounding introduced by the cohort women being healthier, with regard to physical exercise, body mass index and education, the percentage differences for these three factors between the cohort and reference population (Table 5) were calculated, using risk estimates reported in the literature (La Vecchia *et al.* 1987; Berlin & Colditz 1990; Nyboe *et al.* 1989), to produce an index for adjustment of the expected values. The impact of each factor seemed small, since the resulting increase in the relative risk estimates on account of the difference in body mass index was found to be 3%, physical exercise 6%, and education 2%, respectively. Consequently, we do not believe that potential confounding by these factors could account for the observed protective effect of hormones. Admittedly, other subtle but important differences in factors not studied, or known, such as with regard to life style, cannot be ruled out.

Several of our observations support a true biological effect. Firstly, incidence rates of myocardial infarction were similar among those cohort women in the youngest age group as compared with the background population, that is among women most likely to be exposed for only a short duration (Fig. 1); secondly, we found a near baseline risk during the first year of follow-up (Table 4); and, thirdly, in stratified analyses a significantly lowered relative risk occurred only among those prescribed the biologically potent oestrogens (Table 4).

Loss to follow-up due to migration out of the health care region could lead to spuriously few observed cases and underestimation of the risk. However, according to inquiries among a sample of the total cohort in 1986, only 2% were no longer residents in the region (Persson *et al.* 1989). Because the observed outcome would be underestimated by no more than 2–3 cases, the effect on the present risk estimates should be negligible.

Misclassification of exposure based on prescription information could be substantial but would be likely to affect all subgroups equally, entailing an attenuation of true differ-

Table 5. Distribution of specified factors (%) of relevance to the risk of an acute myocardial infarction, among the cohort (653 women) and in the background population (1039 age-matched women), by age (in June 1978).

	<60 years		≥60 years	
Factor	Cohort(%) (528)*	Population(%) (854)	Cohort(%) (125)	Population(%) (185)
History of diabetes	1·5	2·1	4·0	3·3
History of hypertension	15·4	14·7	30·4	28·4
Hysterectomy	19·4	9·3	16·9	9·1
Bilateral oophorectomy	11·6	3·1	7·3	2·8
Quetelet's index†				
<19	6·2	3·6	3·3	8·7
20–24	54·1	45·3	52·0	41·6
≥25	39·7	51·1	44·7	49·7
Smoking				
Never	60·3	65·6	84·4	83·6
Previous	8·9	11·7	7·8	6·0
Current	30·8	22·6	7·8	10·4
Daily physical activity				
Sedentary	5·4	4·6	1·2	3·3
Low	25·2	23·0	15·9	12·3
Moderate	46·7	52·0	68·3	52·4
Heavy	22·7	20·4	14·6	32·0
Daily physical exercise				
None	33·1	34·7	47·7	39·1
Sometimes	26·8	41·5	30·2	47·4
Regular	40·1	23·8	22·1	13·5
Educational level				
<8 years	64·4	68·0	77·9	83·5
8–10 years	23·4	25·4	13·9	13·2
High school	3·8	2·0	3·3	1·0
University	8·4	4·6	4·9	2·2

*No. of women.
†Weight kg/(height m)^2.

ences between exposure groups (bias towards null) (Copland *et al.* 1977). For instance, women classified as users of other oestrogens only could have been exposed to potent compounds, and women 60 years or older could have started their treatment at an earlier age. Also the inclusion of noncompliers (about 9%) in the cohort and some women with exposure to oestrogens in the background population before and after the recruitment period (estimated prevalence of previous usage 12% (Persson *et al.* 1987)) would have decreased any true protective effect of the treatment.

Our results showing a 25–50% decreased incidence of coronary heart disease after exposure to both oestradiol and conjugated oestrogens agree with those of most previously reported prospective epidemiological studies (Stampfer *et al.* 1985; Bush *et al* 1987; Petitti *et al.* 1987; Henderson *et al.* 1988a; Criqui *et al.* 1988; Avila *et al.* 1990; Wolf et al, 1991; Hunt *et al.* 1990). The Framingham Study, however, reported an increased risk of coronary heart disease (Wilson *et al.* 1985), but a re-analysis suggested that oestrogens did not have an adverse effect among women aged 50–59 years (Eaker & Castelli 1988). The Nurses' Health study reported a 50% significant reduction of the risk of nonfatal myocardial infarction or fatal coronary heart disease for ever-users, and a 70% lower risk for current users of conjugated oestrogens (Stampfer *et al.* 1985). The study from the Lipid Research Clinics showed a more than 60% lowered relative risk of death from cardiovascular disease (Bush *et al.* 1987). In the Walnut Creek study the relative risk of death due to cardiovascular disease was 40% below baseline (Petitti *et al.* 1987), and Henderson *et al.* (1988a) found a 40% reduction in the mortality rate and a 29% reduction in morbidity due to acute myocardial infarction among ever-users of oestrogens relative to women who had never taken menopausal oestrogens (Henderson *et al.* 1988a). Further, a meta-analysis of published cohort studies revealed weighted average relative risk estimates ranging from 0·4 to 0·6, depending on type of reference population (Stampfer & Colditz 1991).

Data on the effect of progestogen–combined regimens have hitherto been scanty and have not provided conclusive evidence. A small randomized trial (Nachtigall *et al.* 1979) found no alteration of the risk for myocardial infarction with combined treatment. A case-control study found a slightly increased risk of myocardial infarction and stroke in women prescribed oestrogens alone or progestogens alone and near baseline risk for oestrogen–progestogen combinations. Conversely, a cohort study including some 4500 postmenopausal users of various oestrogen brands, in 43% of their treatments combined with progestogens, reported a significantly 66%

reduced mortality due to ischaemic heart disease (Hunt *et al.* 1990).

An international consensus conference in September 1988 stated that sufficient evidence supports a cardioprotective effect of oestrogen-only therapy in postmenopausal women, but that evidence is insufficient with regard to the protective effects of combined oestrogen–progestogen use (Whitehead & Lobo 1988). It is probable that the protective effect of oestrogens on coronary heart disease is mediated predominantly through a favourable change in the lipoprotein pattern but also through direct effects on the vessel wall physiology (Lobo 1990). However, added progestogens may adversely affect the lipoprotein pattern in a dose and compound dependent manner. Therefore, there is concern that oestrogen–progestogen combined regimens could adversely affect coronary heart disease risk.

We conclude that treatment with potent compounds such as oestradiol and conjugated oestrogens, both alone and maybe also when cyclically combined with progestogens, can reduce the risk of coronary heart disease.

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GYNAECOLOGY

Outpatient falloposcopy: intra-luminal imaging of the fallopian tube by trans-uterine fibre-optic endoscopy as an outpatient procedure

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ABSTRACT

Objective To develop trans-uterine falloposcopy using the linear eversion technique in outpatients.

Design A prospective, descriptive study of the introduction and application of this new technique.

Setting A tertiary referral University Research Clinic independent of operating theatres and inpatient admission.

Subjects Twenty-one infertile women with previous evidence of fallopian tube disease.

Main outcome measures Rate of successful tubal cannulation and procedure completion, tubal section visualized, condition of the tubal epithelium, subsequent treatment plan.

Results A bilateral examination was attempted in 19/21 patients and completed in 18. Two early falloposcopies with inadequate analgesia were aborted due to pain after only one tube had been examined without an attempt to identify or cannulate the contralateral tubal ostium. In one patient, neither ostium was identified or cannulated. After ostial localization, 37/37 tubes were cannulated. If the ostium was not localized but 'blind' cannulation attempted, 1/3 were cannulated successfully. Epithelium characteristic of the ampulla was seen in 31/38 (82%) tubes, and of the proximal tube only in 3/38 (8%). Successful bilateral assessment noted complete bilateral proximal obstruction in 2/18 patients, non-obstructive bilateral endotubal damage in 7/18, unilateral damage in 3/18 and bilateral healthy tubes in 6/18. Unilateral examination in two patients found minimal evidence of damage in one and severe intra-tubal adhesions in the other. After falloposcopy, 11/21 patients elected for IVF, 9/21 tubal surgery and 1/21 for IVF whilst awaiting surgery.

Conclusion Falloposcopy is a technique which can be performed in an outpatient clinic. It is well tolerated, and high rates of luminal cannulation and visualization are possible. Atraumatic access to the tube and visualization of its lumen offer exciting opportunities for diagnosis and treatment of tubal conditions.

Conventional methods of assessing tubal causes of infertility are incomplete as they can only give indirect information about the fallopian tube lumen. Tests of tubal patency give little information regarding the more subtle, dynamic role of the endosalpinx in reproductive function. Hysterosalpingography (HSG) outlines the tubal lumen, laparoscopy allows external observation of the tube and other pelvic organs and salpingoscopy enables observation of the endosalpingeal mucosa for at least the outer one third of the fallopian tube. Tubal factors are implicated in up to 40% of infertility couples (Speroff *et al.* 1983) and treatment options may include surgery or *in vitro* fertilization (IVF) with intra-uterine or tubal transfer of embryo or gametes.

Visualization of the lumen of the proximal segment of the tube may assist in planning rational treatment, allowing for surgery or tubal transfer of embryo or gametes if the mucosa is normal and IVF with intra-uterine embryo transfer if significant disease is present. This may help maximize pregnancy rates (Medical Research International & The Society for Assisted Reproductive Technology 1992) whilst minimizing the risk of ectopic pregnancy. Furthermore, morbidity associated with unsuccessful surgery and subsequent time spent attempting pregnancy will be avoided.

Falloposcopy is the trans-cervical endoscopic examination of the fallopian tube. If it can be performed without anaesthetic in an outpatient setting, the need for operating theatre time and general anaesthesia would be avoided. Costs would be minimized and the risks and morbidity associated with

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general anaesthesia averted. Hence, falloposcopy would be more affordable and more available for the investigation of tubal infertility. This paper describes our initial experience with falloposcopy in a specifically designated outpatient facility, using only oral analgesics, N_2O/O_2 mixture (Entonox, BOC Medical Gases, BOC Ltd, Guildford, Surrey) and paracervical 1% lignocaine.

Subjects and methods

Patients with a history of infertility and evidence of tubal disease on either HSG or laparoscopy were counselled and offered falloposcopy as part of their evaluation. A consulting room in the outpatient clinic was fitted with an adjustable couch designed specifically for gynaecological examination. A Sims speculum was used to identify the cervix and then the vagina and cervix were cleaned with aqueous 15% cetrimide/1·5% chlorhexidine gluconate solution (Savlon Hospital Concentrate, ICI Pharmaceuticals, Wilmslow, UK). The anterior lip of the cervix was gently grasped with a single tooth tenaculum prior to sounding of the cervix with a malleable uterine sound, confirming adequate cervical dilatation to allow easy passage of the catheter used for falloposcopy.

The recently developed linear eversion catheter system (Imagyn Medical Inc., Laguna Niguel, California, USA) for falloposcopy (Bauer *et al.* 1992), can be used without the need for hysteroscopy due to its unique characteristics (Fig. 1) The design of the introducing catheter used to cannulate the tube and 'carry' the endoscope is unique. The catheter has an outer plastic polymer body of 2·8 mm diameter (8·5 French) and a sliding stainless steel inner body of 0·8 mm diameter These are connected at their tips by a polyethylene membrane or balloon some 20 cm long and 50 μm thick. There is a closed space confined by the outer and inner bodies and the membrane ('the balloon space'), to which access is gained via a Luer Lock tap near the rear of the outer body. A fluid filled syringe fitted with a pressure gauge is attached to this tap and allows the pressure within this space to be controlled. Instillation of fluid will increase the pressure in the balloon whilst aspiration will decrease it and even create a vacuum.

Elevating the pressure in the balloon space with the inner body tip less than 20 cm behind the outer body tip results in the membrane everting beyond the end of the catheter as a balloon-like tube with a pressurized two-layered wall (Fig. 1). This everted tube can be advanced by sliding the inner body forward whilst maintaining the position of the outer body and the pressure within the membrane.

The outer catheter body is angulated such that it is directed naturally toward the uterotubal ostium (Fig. 2). Once in position, the eversion membrane is unrolled into the fallopian tube without exerting any shear forces on the epithelium, minimizing the risk of damage and allowing the everting membrane to follow the path of least resistance and negotiate any tortuosity present (Fig. 3). A longitudinal wire is incorporated into the balloon space and connected to a sliding mandril on the outside of the catheter (Fig. 1). Sliding the wire forward straightens the catheter angulation allowing easier introduction through the cervix. Once passed through the cervix the wire is withdrawn to its original position, allowing the catheter to resume its angulated shape (Fig. 2). Next, the 0·48 mm fibre-optic endoscope (FS-300, Imagyn Medical Inc., Laguna Niguel. California) is advanced within the inner body and the polyethylene membrane as far as the tip of the outer body. The catheter and endoscope can then be advanced together with direct visualization through the open end of the catheter tip If not immediately identified, the ostium of the tube can be found by rotating the catheter whilst exerting gentle traction on the tenaculum to stabilize the uterus. Once the ostium is identified, the catheter tip is held in position, the pressure in the balloon space is increased and the balloon membrane everted into the ostium and fallopian tube.

Once the tube has been entered and the eversion balloon advanced a short distance (1–2 cm), the endoscope is passed down the lumen of the unrolled membrane to its tip. The image obtained is displayed on a high resolution colour monitor allowing visualization and confirmation of successful tubal cannulation. The balloon and endoscope can be advanced up to 10 cm in small increments, taking care to keep the tip of the endoscope within the everting membrane to prevent its sharp point from sticking into the tubal wall. Difficulty advancing the balloon and endoscope once the tubal has been entered suggests either obstruction or gross tube tortuosity. Visualization at this point enables the reason for the resistance to be established.

Access to the central lumen carrying the endoscope is pro-

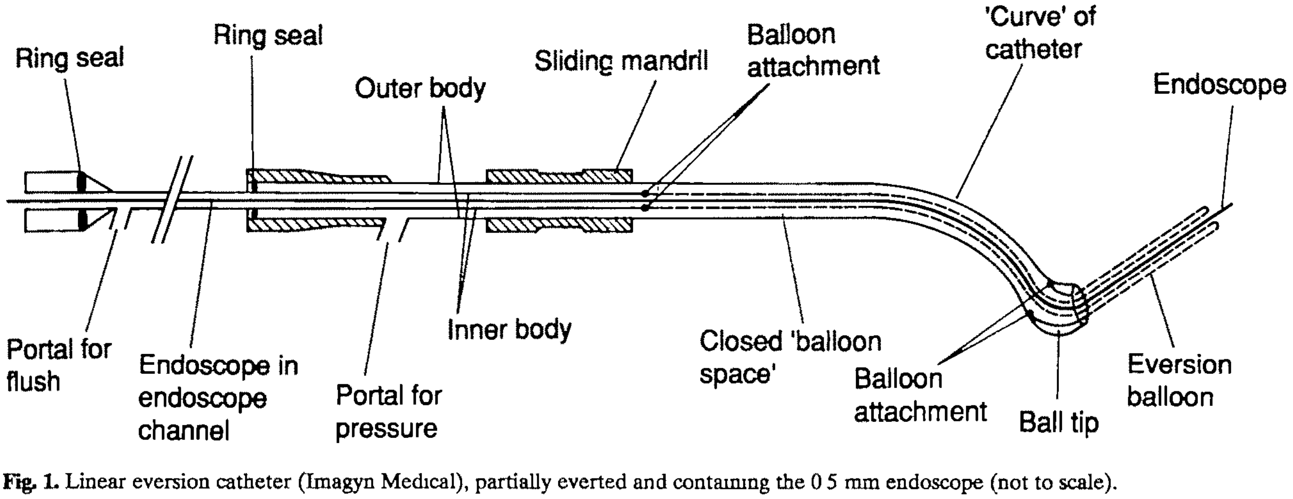

Fig. 1. Linear eversion catheter (Imagyn Medical), partially everted and containing the 0·5 mm endoscope (not to scale).

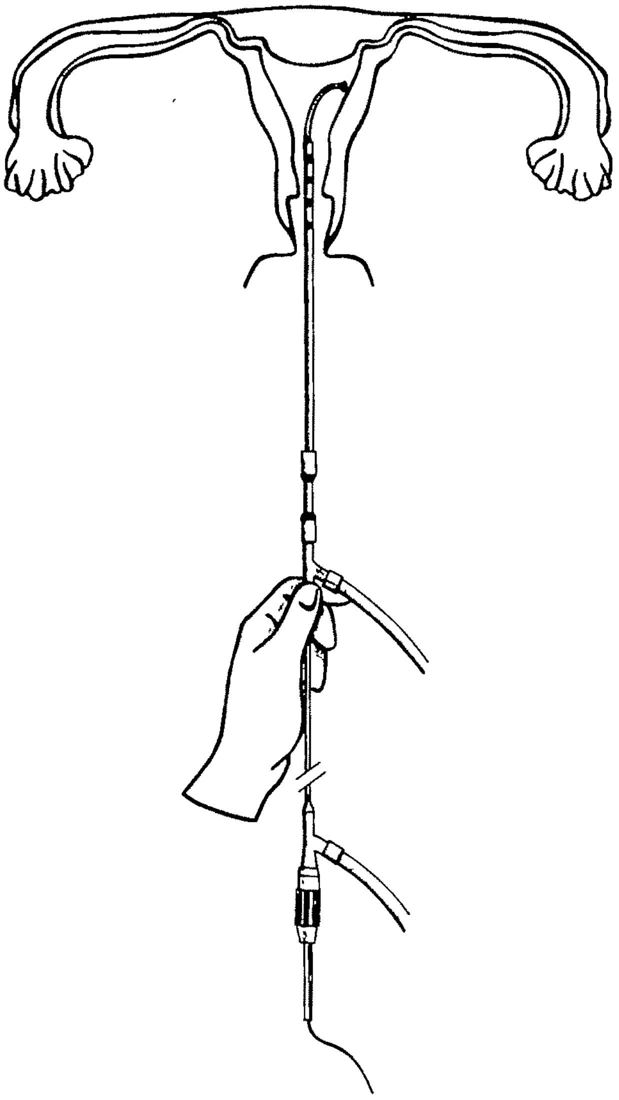

Fig. 2. Falloposcopic system following passage through the cervix and withdrawal of the mandril to allow the catheter curve to reform and direct the tip toward the ostium. The catheter must be advanced to identify the ostium prior to eversion.

vided by a Luer Lock portal at the rear end of the stainless steel inner body (Fig. 1). A peristaltic pump (VS-400, Imagyn Medical Inc , Laguna Niguel, California) is used to flush the central lumen and fallopian tube with an isotonic crystalloid solution. This provides lubrication to facilitate passage of the endoscope and lifts the tubal epithelium away from the lens, thus improving the visual image. The flush can be at a low rate ('default' setting 7 ml/min) or supplemented by a higher rate of bolus flow ('default' setting 15 ml/min). The settings can be changed before or during a procedure with a range of 1–30 mls/min. The pump also has a cumulative flow display for the total volume of fluid delivered since the pump was last turned on or the display cleared.

If the endoscope lens abutts on tissue, reflected light causes the image to 'flare' with loss of definition. A dedicated camera and metal halide arc light source (VS-100 & VS-200, Imagyn Medical Inc., Laguna Niguel, California) compensate for this by providing 'damping' of the light source intensity if significant flare-back occurs, thus decreasing the amount of reflected light. A high resolution colour monitor is used to display the image obtained, allowing visualization by both the operator and patient of the inside of the fallopian tube. Generally the best images are obtained during withdrawal of the everted membrane and endoscope together from the distal point of eversion in the tube. Care must be taken to keep the endoscope level with the tip of the reverting membrane, as failure to do this will compromise the image obtained. A gentle flush is used as necessary to prevent the image from being lost by direct contact with the epithelium.

The fallopian tube can be visualized throughout its length during withdrawal of the endoscope and everted balloon. Once the membrane and endoscope are fully withdrawn into the catheter it can be turned through 180° for use in the contra-lateral tube or removed from the uterus if the procedure is complete. The investigation is recorded on video-tape for subsequent review and the patient is counselled regarding the findings prior to leaving the clinic.

Analgesia

The first three women were given only Entonox as analgesic cover for the procedure. The next four women were premedicated with two tablets of 10 mg dihydrocodeine tartrate/500 mg paracetamol (co-dydramol). In these four 5 ml of 1% lignocaine was infiltrated into each uterosacral ligament immediately prior to starting the procedure. The final 14 patients were prescribed 1 g (2 × 500 mg) of naproxen (Naprosyn, Syntex Pharmaceuticals, Berks, UK) either by their general practitioner or at a previous clinic appointment. This was taken as a single dose at home 90 min prior to the appointed time for falloposcopy. The women were instructed to bring another person with them to the clinic, usually their husband or other close relative or friend. Temazepam (Normison, Wyeth Laboratories, Berks, UK), 20 mg orally (10 mg chewed, 10 mg swallowed whole) was given on arrival in the clinic 15 min before commencing. Uterosacral infiltration with lignocaine was also used in these patients.

The time taken for a bilateral procedure was approximately 35 min. The range was 25–50 min with the analgesia protocol developed sufficient for this period. Paradoxically, it is important to take time over the procedure as haste may lead to disorientation of the balloon tip and the endoscope as well as needlessly increasing the discomfort felt by the patient. The woman's blood pressure is taken every 10 min during the falloposcopy and she is allowed to rest 15 min on completion. In all cases, the woman was lucid, comfortable and able to depart with her husband, other relative or friend within 30 min of leaving the examination couch. Whilst not all patients have been reviewed, we are not aware of the any post-falloposcopy complications.

Results

The results of outpatient falloposcopy in the first 21 patients are reported. The 21 procedures are summarized in Table 1. In two patients (patient nos 2 & 3), only unilateral cannulation was attempted because of significant discomfort. Neither of these patients was premedicated and both were

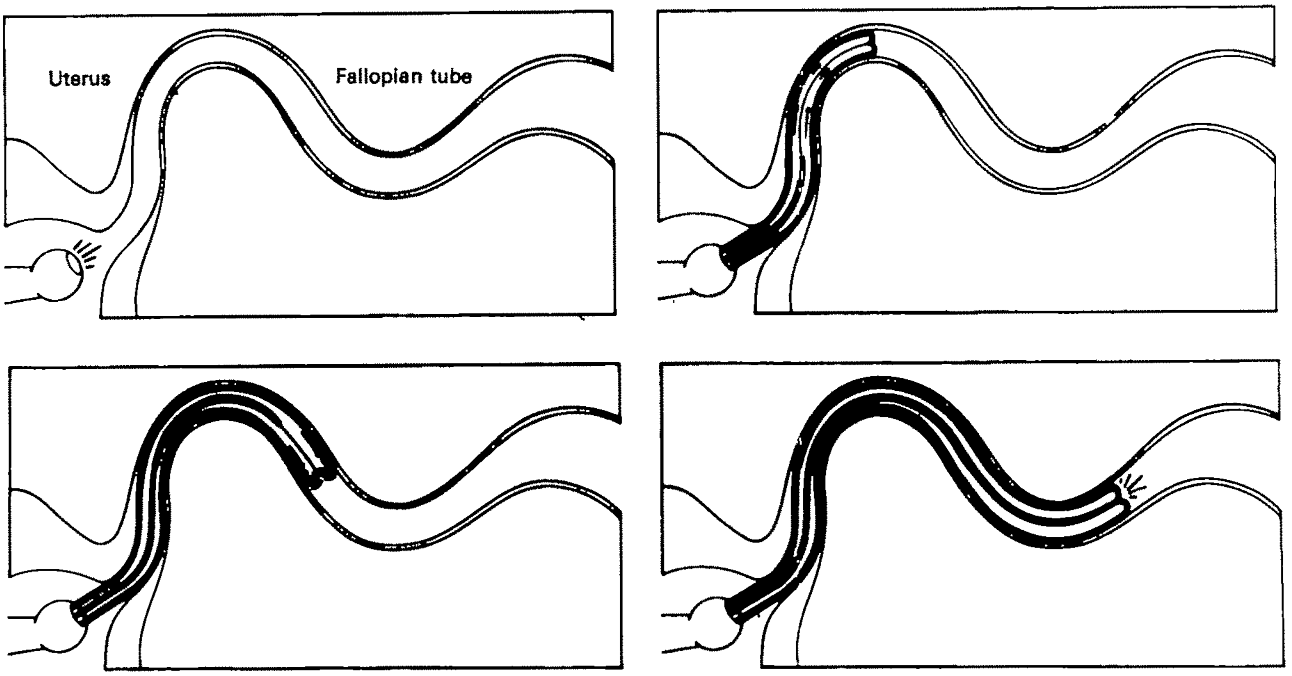

Fig. 3. Eversion of the 'balloon' cannulates the tube and carries the endoscope along with minimal risk of trauma even in a tortuous segment. The sequence shown is read from left to right and demonstrates progressive eversion of the 'balloon' into the tube carrying the endoscope with it.

given Entonox alone as an analgesic. In a third patient, (patient no. 4), with previously diagnosed bilateral proximal obstruction on HSG and laparoscopy, neither ostium could be identified and attempts to cannulate both tubes were unsuccessful. Overall, of 40 attempts to locate an ostium, 37 were successful. In all of these the tube was entered, however, in the three cases of 'blind' attempted cannulation where the ostium had not been located, only one was successful.

Following successful cannulation, ampullary epithelium was identified in 31 out of 38 tubes. In two patients, (patient nos 13 & 19), a complete fibrotic obstruction was encountered in the intramural section of each tube. In the right tube of patient no. 13, the eversion balloon and endoscope passed through the obstruction into the isthmic tube. There was severe scarring and adhesion formation in this section of the tube, suggesting that a segmental resection and anastomosis was unlikely to be successful because of the gross tubal damage present. The left tubal obstruction was impassable. Only the more proximal isthmic and intramural segments could be seen in the remaining three tubes examined (patient nos 2, 9 and 16). Factors contributing to this included tubal tortuosity (perhaps due to extra-tubal adhesions) and consequent difficulty with eversion, relative inexperience with the technique and patient discomfort.

In all cases, the woman was able to describe the sensation and discomfort felt low in the pelvis during the falloposcopy. Sensation was felt to the side of the examination once the tube had been entered, and was useful in confirming tubal cannulation prior to continuing eversion. The most disturbing feeling was felt during higher rates of saline flush This was felt a little higher in the abdomen and was similar to the peritoneal discomfort associated with injection of contrast material during HSG. It could be minimized by using low rates of flush sparingly. Whilst uncomfortable for the woman, the recognition of symptoms is a useful method of assessing the position of the eversion membrane and the success of cannulation.

Entonox alone as analgesia was found to be inadequate and discomfort led to two of the first three patients having the procedure aborted with only one tube examined. Adding premedication with oral dihydrocodeine/paracetamol and paracervical local anaesthesia improved tolerance of the falloposcopy markedly. Subsequently a prostaglandin synthetase inhibitor (naproxen) and a mild, short-acting hypnotic (temazepam) were given as premedication increasing patient comfort still further.

The findings at falloposcopy were scored and recorded on a form designed by Kerin *et al.* (1991). Criteria of disease included patency and degree of dilatation, epithelial appearances and vascular pattern as well as the presence and type of intra-luminal adhesions. Each feature was given a score from 1–3 and the total figure was used to grade the disease as mild, moderate or severe. Two women already described were found to have bilateral complete fibrous proximal obstruction. In seven patients bilateral endotubal disease was graded as severe or moderate/severe. In a further three patients significant unilateral disease was noted with the contra-lateral tube demonstrating an essentially normal appearance. There were severe changes in the tube examined in one of the women who could not tolerate bilateral falloposcopy, whilst in the other woman, the single tube examined appeared healthy. In one woman, no. 4, neither ostium was identified and cannulation was unsuccessful. The remaining six patients had apparently normal tubes on both sides.

The women were told of the findings after the falloposcopy with their accompanying person present. They were able to assess their treatment options with all their investigation results available. It was made clear that the technology is new

Table 1. Outpatient falloposcopy the first 21 cases

Patient number	Tube	Ostium seen	Cannulation attempt	Area in tube visualized				Degree of disease	Planned care	Analgesia
				Intramural	Isthmus	Ampulla	Fimbriae			
1	L	Y	S	Y	Y	Y	N	healthy	micro-surgery	E
	R	Y	S	Y	Y	Y	N	healthy		
2	L	Y	S	Y	Y	N	N	minimal	micro-surgery	E
	R	N	NA	N	N	N	N	—		
3	L	Y	S	Y	Y	Y	N	severe	IVF	E
	R	N	NA	N	N	N	N	—		
4	L	N	F	N	N	N	N	—	IVF	E/C/L
	R	N	F	N	N	N	N	—		
5	L	Y	S	Y	Y	Y	N	severe	IVF	E/C/L
	R	Y	S	Y	Y	Y	N	mild/mod		
6	L	Y	S	Y	Y	Y	N	mod/sev	micro-surgery	E/C/L
	R	Y	S	Y	Y	Y	N	minimal		
7	L	Y	S	Y	Y	Y	N	healthy	micro-surgery	E/C/L
	R	Y	S	Y	Y	Y	N	mod/sev		
8	L	Y	S	Y	Y	Y	N	healthy	micro-surgery	T/Na L/E
	R	Y	S	Y	Y	Y	N	minimal		
9	L	Y	S	Y	Y	N	N	mod/sev	IVF	T/Na L/E
	R	Y	S	Y	Y	Y	Y	mod/sev		
10	L	Y	S	Y	Y	Y	N	healthy	micro-surgery	T/Na L/E
	R	Y	S	Y	Y	Y	Y	healthy		
11	L	Y	S	Y	Y	Y	N	severe	IVF	T/Na L/E
	R	Y	S	Y	Y	Y	N	severe		
12	L	Y	S	Y	Y	Y	Y	minimal	IVF	T/Na L/E
	R	Y	S	Y	Y	Y	Y	moderate		
13	L	Y	S	Y	N	N	N	bilateral proximal obstruct.	IVF	T/Na L/E
	R	Y	S	Y	Y	N	N			
14	L	Y	S	Y	Y	Y	Y	mod/sev	IVF	T/Na L/E
	R	Y	S	Y	Y	Y	Y	mod/sev		
15	L	Y	S	Y	Y	Y	N	severe	micro-surgery	T/Na L/E
	R	Y	S	Y	Y	Y	N	severe		
16	L	N	S	Y	Y	N	N	healthy	IVF	T/Na/L
	R	Y	S	Y	Y	Y	N	min/mod		
17	L	Y	S	Y	Y	Y	N	severe	IVF	T/Na L/E
	R	Y	S	Y	Y	Y	N	severe		
18	L	Y	S	Y	Y	Y	N	healthy	micro-surgery	T/Na L/E
	R	Y	S	Y	Y	Y	Y	healthy		
19	L	Y	S	Y	N	N	N	bilateral proximal obstruct	IVF	T/Na L/E
	R	Y	S	Y	N	N	N			
20	L	Y	S	Y	Y	Y	N	severe	micro-surgery & IVF	T/Na L/E
	R	Y	S	Y	Y	Y	N	severe		
21	L	Y	S	Y	Y	Y	Y	healthy	micro-surgery	T/Na L/E
	R	Y	S	Y	Y	Y	Y	healthy		

All patients had HSG and/or laparoscopic evidence of tubal disease and were candidates for tubal surgery prior to falloposcopy. (L = left, R = right, Y = yes, N = no; S = successful, F = failed, NA = not attempted; Na = naproxen, E = entonox, T = temazepam, L = lignocaine, C = co-dydramol).

and at this stage the meaning of the findings at falloposcopy is not certain. Previously, all women had been anticipating tubal microsurgery but on the strength of all the information available, 11 decided to proceed directly to IVF and 10 elected for microsurgery. One patient chose to pursue IVF whilst waiting for surgical treatment.

Discussion

Minimally invasive diagnostic and therapeutic techniques are becoming increasingly important in gynaecology. There are powerful arguments in terms of expense, patient morbidity and limited resources, for continuing to develop these techniques. The cervix and uterus are easily amenable to cannulation per vaginam for both diagnosis and treatment. In recent years, diagnostic and operative hysteroscopy have developed considerably, however, the fallopian tube has remained largely inaccessible.

Therapeutic options in the treatment of tubal disease often involve a choice between IVF and tubal surgery. Ideally, knowledge of the degree of intra-tubal damage would allow identification of those patients at greatest risk of ectopic gestation or least likely to achieve pregnancy following surgery. HSG provides outpatient assessment of tubal patency and size, but is at best an indirect method of assessing the quality of the endosalpinx and may fail to detect non-obstructive adhesions completely. Laparoscopy allows inspection of the outside of the tubes and pelvic organs and simultaneous trans-cervical chromopertubation is able to assess tubal patency. Salpingoscopy has been reported from several centres (Henry-Suchet *et al.* 1985; Cornier *et al.* 1984; Brosens *et al.* 1987; Shapiro *et al.* 1988; Maguiness & Djahanbakhch 1992), and findings of intra-luminal adhesions and other mucosal abnormalities within the outer part of the tube have been suggested as influencing pregnancy outcomes after surgery (De Bruyne *et al.* 1989). Whilst these methods can be of some value in assessing the prognosis for groups of patients with characteristic findings (Singhal *et al.* 1991), little direct information is obtained about the endosalpinx.

The proximal section of the fallopian tube has been the last part of the female reproductive tract to be assessed by endoscopy. Early attempts had limited success as optical quality was poor and the endoscope diameter was too wide to allow comfortable cannulation of the narrow proximal tube (Mohri *et al.* 1970). Despite the previous assertion, based on fresh dissection of hysterectomy specimens, that guidewire cannulation was risky and doomed to failure (Sweeney 1962), this was accomplished by several authors and used in the diagnosis and treatment of proximal tubal occlusion (Platia & Krudy 1985; Novy *et al.* 1988). Novy *et al.* (1988) used fluoroscopic catheterization techniques to demonstrate patency in up to 84% of apparently obstructed tubes. Confirmation that apparent tubal obstruction is not necessarily irrevocable has been provided by histological examination of proximal tubal segments resected for obstruction diagnosed by HSG and laparoscopic assessment (Sulak *et al.* 1987). In 11 of 18 cases, the proximal segments were found to be patent. Only seven had histological tubal occlusion confirmed.

Falloposcopy as originally developed by Kerin *et al.* (1990) uses a technique termed 'coaxial' cannulation to introduce the endoscope into the fallopian tube. This requires initial tubal cannulation with a flexible guidewire under direct hysteroscopic control, followed by passage of a flexible Teflon cannula over the guidewire into the tube. The endoscope is passed into the cannula after the guidewire has been removed.

Using this technique, Kerin *et al.* (1992) have reported on 112 successfully examined fallopian tubes selected for evidence of endotubal disease on hysterosalpingography. The scoring system briefly described earlier in this paper was developed and used in their series, allowing grading of endotubal disease based on endoscopic appearances. The criteria for normality had been previously described (Kerin *et al.* 1990). The series found normal falloposcopic appearances in 46% of tubes examined despite previous HSG and laparoscopic chromopertubation suggesting absence of fill or spill. Mild/moderate disease was noted in 29% of tubes and severe/obstructive disease in 25%. These gradings of disease severity correlated well with 12 month pregnancy rates of 21%, 9% and 0% respectively.

As well as confirming that many patients with apparent tubal obstruction actually have patent tubes, falloposcopy has been successful in confirming the presence of endotubal isthmic plugs as a cause of reversible tubal obstruction (Kerin *et al.* 1991). Histological examination of these plugs reported them to be composed of 'aggregates of histiocytic-like cells of endometrial stroma or mesothelial origin'.

There appear to be a number of advantages to the linear eversion system of falloposcopy. The eversion catheter protects the tube from the fine endoscope, and prevents the endoscope from directly abutting against folds of epithelium. The 'inflating balloon' nature of the everting membrane means that no shear forces are exerted on the tubal epithelium. This minimizes the risk of any tubal damage and allows the 'balloon' to gently lift the mucosa out of its path as it unrolls, giving the best chance of cannulating the tube atraumatically and negotiating tortuosity and strictures. Almost certainly, many patients with presumed proximal obstruction will be found to have patent tubes by this method. The falloposcopy will then provide further information about the state of the endosalpinx for further management. The access gained to the tubal lumen may then be used as a delivery route for gametes or pharmacological preparations, or perhaps to sample the local environment.

The maximum advantage from the application of falloposcopy will be achieved if it can be established as an outpatient procedure. If specific endotubal information is reliably obtained then HSG may become more of a screening procedure. The women can see the picture on the video monitor, increasing their involvement in their investigation and assisting in counselling. A video recording can be stored and utilized for counselling or review. Avoiding the need for general anaesthesia has obvious medical benefits for the patient, and increases the practicability of the procedure.

Successful outpatient falloposcopy will require a dedicated strategy. We have taken a team approach with designated staff who are experienced in the medical and psychological needs of infertile couples undergoing stressful and sometimes uncomfortable investigations. A purpose-fitted room must be available with a comfortable and relaxing atmosphere. A couch designed for minor gynaecological procedures provides good access to the patient whilst maximizing her comfort. Simple things such as music and wall hangings may make a difference to patient anxiety levels.

Falloposcopy is best learnt by gaining an understanding of the technique from *in vitro* work supplemented by performing cases under general anaesthesia. It is not a technique to be learnt in the outpatient setting as an obviously capable and confident operator is important to engender patient confidence.

Expensive disposable equipment is necessary; however, the cost of this is likely to decrease as the technique becomes more widely used. There are large potential savings in both financial and human terms if surgery which is unlikely to succeed can be avoided. Inpatient time, surgical morbidity and 'time off work' will be minimized, and delay in referral for IVF caused by a failed attempt at surgery may be avoided.

Adequate analgesia is paramount for outpatient procedures. Naproxen and intra-cervical local anaesthetic have been shown to be useful in minimizing discomfort at HSG (Lorino *et al.* 1990). A similar approach seems to be effective for falloposcopy although continued assessment and refinement of analgesia provision is critical. There have been no reported cases of sepsis following falloposcopy in over 200 cases that have been performed to date, using various techniques. Aseptic technique, which is similar to that for HSG or for minor surgical procedures in the operating theatre, is used. The disposable eversion catheter is supplied sterile, a sterile isotonic crystalloid is used to flush and the endoscope is immersion sterilized.

Falloposcopy using the linear eversion technique now allows reliable access to the lumen of the fallopian tube and imaging of the endosalpinx. We are now performing it routinely in an outpatient setting, having devolved from initial work in the operating theatre. We are encouraged by the tolerance of our patients for the procedure, as well as by the success rates of cannulation and visualization. Given further experience with the technique, and refinement in the analgesia provided, we hope to improve these aspects of performing falloposcopy by this method. It is our aim to perform all falloposcopy without any need for recourse to general anaesthesia.

Information gained from the procedure is an aid to patient counselling. Overall, falloposcopy is likely to promote better treatment for our patients and cost-savings to the community.

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REPRODUCTIVE SCIENCE

Intergenerational studies of human birthweight from the 1958 birth cohort.
II. Do parents who were twins have babies as heavy as those born to singletons?

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ABSTRACT

Objective To ascertain whether maternal twinning influences the previously described association between the birthweight of singleton mothers and their infants.

Design and subjects The association between the birthweight of singleton parents and their offspring and that between twin parents and their offspring was compared using data from the 23-year-old sample of the 1958 British national birth cohort. The numbers available for full comparison were 1027 female and 611 male singleton cohort members, and 26 female and 17 male twin cohort members and their first singleton livebirths.

Results Of the mothers who had been twins, half had been of low birthweight, and overall their mean weight was 700 g less than that of their singleton counterparts. Nevertheless, the mean birthweight of babies of twin mothers was 133 g, and of twin fathers 94 g, greater than of babies of corresponding singletons. For female, but not male, parents this difference persisted after adjustment for confounding variables.

Conclusions We suggest two possible reasons for the difference between the weight of babies of twin and singleton mothers. Firstly, the growth of twins becomes retarded late in pregnancy, possibly after a period critical in determining long-term reproductive effects. Secondly, the twin survivors were of higher birthweight than the original twin cohort, whilst the singleton survivors were more representative of all singleton births, thus introducing a possible bias.

In a previous communication (Emanuel *et al* 1992) results were presented from the 23-year follow-up of the singletons in the 1958 national birth cohort (generated by the National Birthday Trust Perinatal Mortality Survey in 1958 and followed up with National Child Development Study, NCDS) and their babies, which confirmed previous reports of the positive influence of parental birthweight on the birthweight of their offspring. This effect remained even after allowing for a number of confounding factors. That sample was limited to those where both the cohort member and their babies had been singleton births.

However, Magnus *et al.* (1985) reported that women who were born one of a twin pair and therefore often of low birthweight, had babies with birthweights similar to those of the babies of singletons. Also, that where the birthweight of twin pairs had been discordant, the birthweights of offspring of the larger twin did not differ significantly from those of the offspring of the smaller twin This paper reports the comparison of the birthweight of the offspring of twin and singleton cohort members born by the time of the 23-year follow-up of the 1958 birth cohort.

Subjects and methods

Details of the sample and methods have been published previously (Alberman *et al.* 1991; Emanuel *et al.* 1992), but will be described briefly below.

The birth of the cohort members

The cohort began with the National Birthday Trust Fund Perinatal Mortality Survey (Butler & Bonham 1963; Butler & Alberman 1969), a study of all births in England, Wales and Scotland during the week of March 3–9, 1958. The cohort was followed up at 7, 11, 16 and 23 years. At the last follow-up in 1981 at age 23 years (NCDS-4) there was a 72% response of

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the original cohort members, excluding those who had died or emigrated (Shepherd 1985).

Twenty-three-year follow-up

In 1981 a large body of information was collected on the socioeconomic, educational and health status of the cohort members, and on the survival, sex, birth order, multiplicity and birthweight of all children born to them up to that time. The gestational age of the children was not asked. Most of the relevant data were not available for the mothers of the children of the male cohort members (their spouses or partners) nor for the fathers of the children of the female cohort members.

Numbers in the analyses

This report relates only to caucasian cohort members followed at 23 years and, to simplify the analyses, is confined to their first liveborn singleton births. There were 135 twin female cohort members contacted who had reported 42 first born live singletons, and of 131 male twin cohort members contacted, 27 had fathered first born live singletons. Singleton female cohort members reported 1949, and male cohort members 1039, corresponding births.

For the regression analyses there were a number of sequential exclusions because of missing data, shown in Table 1, leaving 1027 female and 611 male singleton cohort members and their first singleton livebirths, and 26 female and 17 male twin cohort members and their first singleton livebirths. Whatever the biases resulting from the exclusions these should apply equally to the twins and singletons. It must be remembered that the samples are only of surviving cohort members and, particularly in the case of the twins, are not representative of the original births sample.

Notation

To simplify their description, parents of the cohort members are designated as the F1 generation, the cohort members as the F2, and their offspring as the F3 generation, although the associations described are not necessarily genetic.

Statistical methods

The effect of parental and grandparental characteristics on F3 birthweight was examined by descriptive analyses, and by multiple regression, using the statistical package GLIM (Aitkin *et al.* 1989). Model simplification was achieved by backward elimination from the maximal model. All models include a measure of 'goodness of fit', represented in this account by the residual standard deviation.

Results

Birthweight and gestational age

Table 2 shows that, at their own birth, cohort members who were twins had markedly lower mean birthweights and a shorter mean gestational duration than singletons, and about 50% had weighed under 2500 g. Compared with singleton birthweight centiles for sex in the original birth cohort, 47% of the female twins and 23% of the male twins had weights under the 10th, and 72% of the females and 50% of the males had weights below the 25th centile. In spite of these differences in the parents, the mean birthweight of babies of female twin cohort members was 133 g heavier than that of female singletons, and that of babies of male twins 94 g heavier than that of male singletons.

Table 3 contains many of the same comparisons for the smaller sample for whom full intergenerational data were available which, as before, shows the increased birthweight in the babies of a twin parent, particularly twin mothers. This also shows that the mean adult weight of the cohort members who had been twins was slightly, but not significantly, less than that of singleton cohort members, although their heights were similar.

These findings were further examined using multiple

Table 1. Available data for total singleton and twin sample and totals remaining after sequential exclusion of cases with missing data.

	Males				Females			
	Singleton (*n* = 1039)		Twin (*n* = 27)		Singleton (*n* = 1949)		Twin (*n* = 42)	
	Valid *n*	(Missing) *n*	Valid *n*	(Missing) *n*	Valid *n*	(Missing) *n*	Valid *n*	(Missing) *n*
F3 Baby's birthweight (g)	990	(49)	25	(2)	1942	(7)	42	(0)
F3 Baby's gender	990	(0)	25	(0)	1940	(2)	42	(0)
F2 Mother's birthweight (g)	918	(72)	24	(1)	1816	(124)	40	(2)
F2 Mother's gestation (days)	807	(111)	22	(2)	1594	(222)	36	(4)
F2 Mother's non-pregnant weight (kg)	797	(10)	22	(0)	1565	(29)	34	(2)
F2 Mother's adult height (cm)	790	(7)	22	(0)	1557	(8)	34	(0)
F2 Father's social class	673	(117)	17	(5)	1151	(406)	29	(5)
F1 Grandfather's social class	636	(37)	17	(0)	1084	(67)	29	(0)
F1 Grandmother's height (cm)	615	(21)	17	(0)	1042	(42)	27	(2)
F1 Grandmother's non-pregnant weight (kg)	611	(4)	17	(0)	1027	(15)	26	(1)
Total with data	611		17		1027		26	

Table 2. Descriptive variables for total singleton and twin sample.

		Males		Females	
		Singleton (n = 1039)	Twin (n = 27)	Singleton (n = 1949)	Twin (n = 42)
F2 Cohort member	Gest. <37 weeks				
	%	5·6	30·4	3·6	10·8
	(No. known)	(875)	(23)	(1637)	(37)
F2 Cohort member	BW <2500 g				
	%	4·5	48	7·0	50
	(No. known)	(963)	(25)	(1824)	(40)
F3 Baby	BW<2500 g				
	%	7·7	8·0	8·3	0
	(No. known)	(990)	(25)	(1942)	(42)
F2 Cohort member	Mean BW (g)	3416	2587	3251	2550
	SD	517	521	502	544
	(No. known)	(963)	(25)	(1824)	(40)
F2 Cohort member	Mean gestation (days)	281	266	282	274
	SD	13·2	23·1	12·8	13·4
	(No. known)	(875)	(23)	(1637)	(37)
F3 Baby	Mean BW (g)	3251	3345	3216	3349
	SD	541	490	550	390
	(No known)	(990)	(25)	(1942)	(42)

BW = birthweight; Gest = gestational duration.

regression to allow for possible confounding influences of parental or maternal grandparental height, weight and social class, and babies' sex. Table 4 shows the final model for the regression on birthweight of the variables described for babies of the female and male cohort members separately. For the babies of the female cohort members, the fact of the mother having been a twin was associated with a significantly higher birthweight after adjusting for the joint effects of all other variables, including the mother's own birthweight and gestational age. The adjusted difference is 239 g (95% CI: 25

Table 3. Descriptive variables for singleton and twin sample (All values known).

		Males		Females	
		Singleton (n = 611)	Twin (n = 17)	Singleton (n = 1027)	Twin (n = 26)
Baby—F3	Mean BW (g)	3235	3295	3230	3391
	(SD)	(541)	(552)	(556)	(372)
Cohort member—F2	Mean BW (g)	3416	2553	3250	2618
	(SD)	(516)	(493)	(496)	(542)
Cohort member—F2	Mean gestation (days)	281	266	282	275
	(SD)	(13)	(20·4)	(12·4)	(13·5)
Cohort member—F2 at 23 years	Mean weight (kg)	73·4	68·0	58·7	56·5
	(SD)	(10·7)	(7·6)	(9·0)	(8·0)
Cohort member—F2 at 23 years	Mean height (cm)	176·6	176	160·9	161
	(SD)	(7·0)	(5·1)	(6·5)	(6·8)
Grandmother—F1	Mean height (cm)	160·5	160·8	160·7	161
	(SD)	(6·2)	(6·1)	(6·6)	(6·3)
Grandmother—F1	Mean weight (kg)	60·0	60·3	59·3	60·6
	(SD)	(10·7)	(10·5)	(9·7)	(11·6)
Categorical variables		n (%)	n (%)	n (%)	n (%)
F3 Baby gender	M	322 (53)	7 (41)	520 (51)	12 (46)
	F	289 (47)	10 (59)	507 (49)	14 (54)
F2 Parent—Social class	Non-manual	118 (19)	1 (6)	241* (24)	11* (42)
	Manual	493 (81)	16 (94)	786 (76)	15 (58)
F1 G'parent—Social class	Non-manual	95 (16)	2 (12)	178 (17)	6 (23)
	Manual	516 (84)	15 (88)	849 (83)	20 (77)

*Spouse or partners 1980 social class.

Table 4. Multiple regression models predicting F3 babies' birthweight. Female and male cohort members and their first births.

Final model									
Significant predictors	*Interval/Level*	*Regression coefficient (SE)*							
Sex of twin parent		*male*		*female*		*male*		*female*	
Sample size		628	(SE)	1053	(SE)	*t-value*	*P-value*	*t-value*	*P-value*
Constant		2564	(184·3)	2275	(548·1)				
F2 Birthweight	per 100 g	11	(4·1)	19	(3·5)	2·66	0·008	5·33	<·0001
F2 Adult weight	per 10 kg	49	(20·4)	84	(18·5)	2·42	0 015	4·52	<·0001
F3 Baby's gender	female *vs* male	–119	(42·7)	–98	(32·4)	–2 79	0·005	–3·01	003
F2 Mother's gestation	per day	—		–4	(1·4)			2·94	·003
F1 Grandmother's height	per 10 cm	—		77	(25·5)			3·00	·003
F1 Grandfather's social class	manual *vs* non-manual	—		–95	(43·2)			–2·20	028
F2 Father's social class†	manual *vs* non-manual	—		–158†	(38·4)			–4·12	<·0001
F2 Multiplicity	twin *vs* singleton	—		239	(106·7)			2·24	025
Residual standard deviation		531·7		524·3					
Predictors dropped from 'current' models, in descending order.									
F2 Female model									
F1 Grandfather's social class* F2 Father's social class†								0 59	0·56
F1 Grandmother's non-pregnant weight (kg)								–0·12	0·90
F2 Mother's adult height (cm)								1·10	0·27
F2 Male model									
F1 Grandfather's social class* Father's social class†						0·48	0·63		
F2 Father's social class (manual *vs* non-manual)						–0·09	0·93		
F1 Grandfather's social class (manual *vs* non-manual)						0 30	0·76		
F1 Grandmother's height (cm)						–0·43	0·67		
F2 Father's adult height (cm)						0·45	0·65		
F2 Father's gestation (days)						–1·23	0·22		
F1 Grandmother's non-pregnant weight (kg)						–1·22	0·22		
F2 Multiplicity (twin *vs* singleton)						1·54	0·12		

*Interaction between covariates.
†Spouse or partners 1980 social class.

to 453) for the babies of twin mothers. The difference for babies of twin fathers was 209 g which was not statistically significant (95% CI: –61 to 479).

Discussion

Studies from different populations have found that deficits in intrauterine growth of females are related to suboptimum reproductive outcome in the next generation (Ounsted & Ounsted, 1973; Hackman *et al.* 1983; Toth *et al.* 1983; Klebanoff *et al.* 1984; Ounsted *et al.* 1986; Emanuel 1986; Klebanoff & Yip 1987; Langhoff-Roos *et al.* 1987; Klebanoff *et al* 1989; Emanuel *et al.* 1989; Emanuel (in press); Alberman *et al.* 1992). However, Magnus *et al.* (1985) reported that the birthweights of babies of twin parents were similar to those of the general population of births in Norway. No differences were found between the birthweight or gestational duration of babies of monozygotic female twins whose own birthweights had differed by at least 300 g, the mean birthweight of the offspring of the larger twin being 3537 g (SEM 40 g) and of the smaller twin being 3532 (SEM 43 g). They questioned whether the long term effects of low birthweight are the same for twins and singletons. The results reported here suggest that they are not the same.

Although the female twins in this series had experienced a retardation of intrauterine growth, their offspring paradoxically had slightly larger mean birthweights than those of singleton parents. In intergenerational studies of birthweight in three populations (US, Sweden, UK) that utilised multiple regression techniques, when mother's birthweight and mother's adult height were both in the model, the mother's height lost statistical significance (Hackman *et al.* 1983; Langhoff-Roos 1987; Emanuel *et al.* 1992; and Table 4 in this account). This indicates that mother's intrauterine growth is a critical period relative to the intergenerational phenomenon.

However, at least two studies have shown that the mean birthweight of twins (live or stillborn) seems not to deviate from that of singletons until late in pregnancy (McKeown & Record 1951; Naeye 1964). Thus our comparisons of births to twin and singleton mothers point to early gestation of the mother as being the most critical period in respect of intergenerational influence, a suggestion supported by recent findings in regard to the babies of Dutch women who had been exposed *in utero* to the Hunger Winter famine of 1944–1945. Compared with controls, women who had been exposed during the first and second trimesters were more likely to have babies with lower mean birthweight and gestational duration (Lumey 1988). However, the mean birthweight of these women was not different from that of controls, since full nutrition was re-established with liberation, coinciding with the third trimester. On the other hand, the women who had been exposed during their third trimester themselves had smaller birthweights than the controls, but there was no reduction in the birthweight of their offspring.

It is known that insults to the developing embryo during the period of organogenesis can result in gross malformations. It is therefore biologically plausible that less serious insults during the same period can result in alterations to the developing organism resulting in subtle but permanent alterations in the physiology of the fetus. This is a probable mechanism for the intergenerational effect in pregnancy outcome, as well as for other associations between birth size and postnatal health which have been found (Gensser *et al.* 1988; Barker *et al.* 1989a, 1989b; Whincup *et al.* 1989) and others which will undoubtedly be found in the future (Emanuel, in press).

After allowance was made for confounding factors the fact that the father had been a twin did not have a significant effect on the birthweight of his offspring. Whatever the paternal biological contribution, it is most probably strictly genetic. The mother's contribution, which predominates, while partly genetic, is markedly altered by environmental influences, as shown by the relations of birthweight to such factors as maternal age, parity and socioeconomic status (Butler & Alberman 1969; Migone *et al.* 1991). Additionally the intergenerational effect in the determination of birthweight seems to pass through the maternal and not the paternal line (Ounsted *et al.* 1986; Emanuel *et al.* 1992).

It should be noted that all twin parents whose infants have been studied were born before the era of modern obstetric and neonatal care, which began in the mid-1960s. They may represent 'healthy survivors' analogous to the 'healthy worker' phenomenon, but this was true also of the singletons. However, since mortality of twins is greater than that of singletons, it may be that the twin parents in this series are relatively more vigorous 'healthy survivors' than their singleton counterparts.

The current follow-up of the 1958 cohort, now aged 33, will provide data on larger numbers of their offspring, and has included questions about their gestational age. The analysis of the new data will allow the extension of the work reported here. However, it would be important to confirm the present findings in other similar data sets.

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REPRODUCTIVE SCIENCE

A prospective study comparing the outcome of oocytes retrieved in the aspirate with those retrieved in the flush during transvaginal ultrasound directed oocyte recovery for *in-vitro* fertilization

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ABSTRACT

Objective To study prospectively the fate of oocytes collected from the follicular aspirate and subsequent flushes during transvaginal ultrasound directed oocyte recovery for *in-vitro* fertilization (IVF).

Setting A tertiary referral assisted conception centre.

Subjects 100 consecutive patients undergoing 100 cycles of IVF. Four patients were withdrawn because their embryos were electively cryopreserved. Therefore 96 cycles were studied.

Main outcome measures The oocyte recovery rate, viability, fertilization and cleavage rates and outcome of embryos generated from oocytes that were obtained from either the initial aspirate (A1), dead space in the collecting system (A2) or the first two 2 ml flushes (F1 and F2) were compared.

Results The overall oocyte recovery rate was 87·8%. Of the 1046 oocytes collected, 40·3% were from A1, 41·3% from A2, 13·7% from F1 and 4·7% from F2. There were comparable numbers of viable and fertilized oocytes and cleaved, transferred and frozen embryos in tubes A1 and A2 but all these parameters were significantly lower in tubes F1 and F2 ($P<0·0001$). All these parameters were also significantly higher in F1 compared with F2 ($P<0·001$), except for the number of embryos frozen, in which there was no difference. The overall pregnancy rate per cycle was 28·1% and the pregnancy rate per embryo transfer was 31·0%. There were no pregnancies in any of the cycles in which embryos originating from F2 were transferred, nor were there pregnancies in cycles in which only embryos from F1 were transferred.

Conclusion Follicular aspiration together with one 2 ml flush maximises the recovery of oocytes that will result in pregnancies.

In many assisted conception centres, follicle flushing is traditionally employed during transvaginal ultrasound directed oocyte recovery (TUDOR) for *in-vitro* fertilization (IVF) in the belief that flushing allows a significant number of oocytes to be collected which would otherwise be missed if aspiration alone is used. However, a number of recent prospective randomized studies (Haines *et al.* 1989; Scott *et al.* 1989; Kingsland *et al.* 1991; Tan *et al.* 1992) comparing aspiration alone with aspiration and flushing have suggested that there is no significant difference in the oocyte recovery rates using the two techniques. It has also recently been reported that oocytes recovered after multiple flushes are of poor quality and have a reduced fertilization rate (Waterstone & Parsons 1992). The design of the latter study, however, did not permit precise determination of the stage of flushing at which the decline in fertilization rates occurred. Moreover, there is no data of which we are aware that compares the viability and cleavage rates, or the suitability for embryo cryopreservation of oocytes obtained in the aspirate with those obtained in successive flushes. We therefore embarked on a prospective study to compare the quality and outcome of oocytes retrieved in the initial and dead space aspirates with those derived from each successive flush during TUDOR.

Subjects and methods

One hundred consecutive patients undergoing IVF and having TUDOR performed by two of the regular clinic staff (EH and AB) were included in the study.

Ovarian stimulation was achieved in 84 patients with human menopausal gonadotrophin (hMG; Pergonal, Serono,

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Welwyn Garden City, UK) either alone or in combination with 'pure' follicle-stimulating hormone (FSH; Metrodin. Serono, Welwyn Garden City, UK) after pituitary desensitization with the luteinizing hormone releasing hormone (LHRH) agonist, buserelin (Suprefact, Hoechst, Hounslow, UK). Nine patients received buserelin as a 'flare' from day two of their cycle together with hMG ± FSH, two received a combination of clomiphene citrate (CC) and hMG, two received hMG alone (converted from intra-uterine insemination with superovulation) and three received CC alone ('minimally-stimulated' cycles).

The dose of hMG/FSH used was adjusted according to follicular response as determined by serial ultrasound scans. Human chorionic gonadotrophin (hCG; 10 000 IU, Profasi, Serono, Welwyn Garden City, UK) was administered when there were at least four follicles with a mean diameter (measured in three planes) of at least 14 mm and the mean diameter of the largest follicle in CC regimens had reached 17 mm and that of the largest follicle in buserelin regimens 18 mm. Transvaginal oocyte recovery was performed 35 h after hCG administration as an outpatient procedure.

An SDR-1550XP (Phillips, Hammersmith, London) ultrasound scanner with a 5MHz vaginal probe was used for TUDOR. Oocyte recovery was performed using a double-lumen needle (16 gauge, K-OPSD-1632, W. A. Cook, Brisbane, Australia PTY Ltd) and a KMAR 5000 vacuum pump (W. A. Cook, Brisbane, Australia), with an aspiration pressure of −25 KPa. The dead-space in the Teflon tubing was 2 ml and the follicles were flushed with a HEPES-buffered Earles balanced salt solution which contained phenol red as a pH indicator.

Every follicle with a diameter of >10 mm was aspirated. The tip of the needle was directed to the centre of the follicle and the aspirate was considered complete when the follicle appeared to have completely collapsed on the ultrasound scan. This aspirate was labelled tube A1. The test tube was replaced and handed to the embryologist. The dead space in the collecting system (needle and attached tubing) was then flushed with 2 ml culture medium until the first drop of medium was seen. The contents of this second tube were labelled A2. The follicle was then flushed twice with 2 ml of culture medium and these tubes were labelled F1 and F2 respectively. The time was recorded from insertion of the needle into the first ovary until withdrawal of the needle from the second ovary.

All oocytes were examined regularly after insemination and only those in which two pronuclei were seen were considered to have fertilized normally. Between one and three pre-embryos were transferred approximately 48 h after oocyte recovery, by which time they had undergone at least one mitotic division. Luteal support was provided by the administration of hCG and Gestone (progesterone in oil, 100 mg; Paines & Byrne Ltd, Greenford, UK).

Statistical analysis was performed using the two-sample *t*-test and χ^2 test as appropriate. A $P<0{\cdot}05$ value was considered significant.

Results

Four patients were excluded from the study because they were considered to be at high risk of developing the ovarian hyperstimulation syndrome and all their embryos were electively frozen at the pronuclear stage. The mean (± SD) age of the 96 patients who were included in the study was 34·1 (± 4·9) years. In 27% of cases the main diagnosis was tubal damage, 31·2% had male factor infertility, 15·6% unexplained infertility, 4·1% endometriosis, 3·1% anovulatory infertility and 19·8% a combination of these. On the day of hCG administration (mean 11·6 ± 1·6 days) the mean (SD) diameter of the largest follicle was 21·6 (± 2·4) mm and there were eight follicles >14 mm in diameter (Table 1). A mean of 12 follicles were aspirated and the average time (SD) taken for oocyte recovery was 25·8 (± 11·1) min.

The mean (SD) oocyte recovery rate was 87·76 (± 11·8)%. Of the 1046 oocytes collected, 422 were obtained in A1 (40·3%), 432 in A2 (41·3%), 143 in F1 (13·7%) and 49 in F2 (4·7%). The mean number of oocytes collected in tubes A1 and A2 were significantly greater than that collected in tubes F1 and F2 ($P<0{\cdot}00001$, Table 2). There were comparable numbers of viable and fertilized oocytes and cleaved, transferred and frozen embryos in tubes A1 and A2 but all these parameters were significantly lower in tubes F1 and F2 compared with A1 ($P<0.0001$). All these parameters were also significantly higher in tube F1 compared with tube F2 ($P<0{\cdot}001$) except for the number of embryos frozen, in which there was no difference.

The numbers of viable eggs and the percent viability (viable eggs/total eggs) are shown in Table 2. Ninety-six per cent of the oocytes in tubes A1 were viable compared with 89·6% in A2, 83·9% in F1 and 63·3% in F2. There were significantly more viable eggs in A1 than in any of the other samples. Similarly both A2 and F1 contained significantly more viable eggs than F2 ($P<0{\cdot}001$ and $P<0{\cdot}01$ respectively).

The overall fertilization rate (fertilized oocytes/viable oocytes) was 62·7%. Sixty-three per cent of the viable oocytes from A1 fertilized compared with 60·7% of those from A2, 65·8% of those from F1 and 35·5% of oocytes from F2. The fertilization rate was significantly lower for oocytes obtained from F2 compared with the other samples ($P<0{\cdot}01$) and there was no difference between A1, A2 or F1. The cleavage rate of pre-embryos generated from oocytes collected in tube F2 was significantly lower than those from tube A1 or F1 (Table 2).

In this series of 96 treatment cycles there were 27 preg-

Table 1. Results of study

Variables	Mean ± SD*
Age (years)	34·1 ± 4·9
Day of hCG	11·6 ± 1·6
Diameter of largest follicle (mm)	21·6 ± 2·4
No. of follicles >14 mm	8·3 ± 3·6
No. of follicles 12–13 mm	4·0 ± 3·3
No. aspirated	12·3 ± 5·8
Time taken (min)	25·8 ± 11·1
No. of oocytes	11·0 ± 5·6
Viable oocytes	9·8 ± 5·0
Fertilized oocytes	6·0 ± 3·6
Cleaved oocytes	4·7 ± 3·2
Embryos transferred	2·4 ± 1·0
Embryos frozen	0·7 ± 1·4

*± standard deviation.

Table 2. Comparison of oocytes obtained from tubes A1 (initial aspirate), A2 (dead space aspirate), F1 (first flush) and F2 (second flush).

Variables	A1	A2	F1	F2
No. oocytes	4·4 ± 3·6	4·6 ± 4·1	1·6 ± 1·6	0·4 ± 1·1
Viable oocytes	4·2 ± 3·5	4·0 ± 3·7	1·3 ± 1·3	0·3 ± 0·9
% viability	96·0%	89·6%^{a}	83·9%^{b}	63·3%^{b}
Fertilized oocytes	2·7 ± 3·0	2·5 ± 2·8	0·8 ± 1·0	0·1 ± 0·4
Fertilisation rate	63·0%	60·7%	65·8%	35·5%^{c}
Cleaved oocytes	2·2 ± 2·6	1·7 ± 2·2	0·7 ± 0·9	0·1 ± 0·3
Cleavage rate	81·6%	69·4%^{c}	89·9%	54·5%^{d}
Embryos transferred	1·0 ± 0·9	0·9 ± 1·0	0·5 ± 0·6	0·02 ± 0·1
Embryos frozen	0·4 ± 1·0	0·2 ± 0·5	0·1 ± 0·2	0·02 ± 0·02

Levels of significance as compared with A1; for other statistics refer to text:
^{a} $P<0·001$; ^{b} $P<0·0001$, ^{c} $P<0·01$; ^{d} $P<0·03$.

nancies (28·1%) and nine cases of failed fertilization, in which the diagnosis was either male factor or unexplained infertility. Thus the pregnancy rate per embryo transfer was 31·0%. The 27 pregnancies arose from the transfer of 76 embryos. This resulted in 16 singleton pregnancies, seven twins, one set of triplets and one set of quadruplets (after the transfer of three embryos). There were two ectopic pregnancies, three miscarriages, 22 patients have now delivered successfully.

Discussion

Since the initial description of the direct transvaginal approach for oocyte recovery under ultrasound guidance (Wikland *et al.* 1985), the method has largely superceded all other approaches for oocyte recovery for IVF. When the technique was first developed a single lumen needle was used. The potential disadvantage of using this needle is that if follicle flushing is used, oocytes not recovered in the initial aspirate may be repeatedly flushed from the dead space of the needle back into the follicle. The use of a double-lumen needle has the advantage of allowing the flushing medium to traverse a different channel, thereby avoiding this problem.

The theoretical advantage of flushing is that it allows the retrieval of a high proportion of oocytes that would otherwise be missed if aspiration alone were used. We achieved an 83·7% oocyte recovery rate by performing one aspirate and two 2 ml flushes (A1, A2 and F1). Others have found no increase in recovery rates when flushing compared with aspiration alone, although their oocyte recovery rates were lower than in our study: 66% (Scott *et al.* 1989), 76% (Haines *et al.* 1989), 75% (Waterstone *et al.* 1992) and 79% (Tan *et al.* 1992). Kingsland *et al.* (1991) do not state their recovery rate but found no difference in the mean number of oocytes retrieved when aspiration only was compared with aspiration and flushing with 10 ml of medium

The obvious disadvantage of flushing is that if it is performed repeatedly, it significantly lengthens the procedure. Since TUDOR is generally performed without general anaesthesia, minimizing the duration of the procedure is important for patient comfort. Moreover, repeated flushing increases the cost of consummables and the work load on the embryologist. Kingsland *et al.* (1991) found that flushing significantly increased the time of the procedure from a median of 20 min with aspiration alone to 35 min when flushing was employed. Tan *et al.* (1992) similarly found that flushing significantly increased the duration of the procedure from 15 to 30 min. The mean duration of our procedures was 25·8 min, which was not significantly longer than our routine practice prior to the study. During the study we waited for the embryologist to examine the contents of each test tube before moving on to the next flush or aspirate. Our results indicate that it is no longer necessary to do this and so the mean duration of our collection time has now been reduced to about 15 min.

We found that 82·3% of the oocytes were collected from the aspirate (A1) and dead space of the collecting system (A2); this was significantly higher than the number of oocytes collected from the first two flushes (F1 and F2). Two other studies have looked at the fate of oocytes from successive flushes employing the same nomenclature for A1 and A2: Waterstone *et al.* (1992) recovered 82·9% of oocytes from A1 and A2, whilst for Tan *et al.* (1992) this figure was 85·5%. In both of these studies the first three flushes were designated as F1 and the next three flushes as F2 and, therefore, it was not possible to determine the outcome of oocytes collected with each successive flush.

It is not possible to make a direct comparison between our study and those of other groups because different calibre needles were used and slightly different techniques were employed. Most groups have simply compared oocyte recovery and fertilization rates between aspiration alone and aspiration with flushing (Haines *et al.* 1989; Scott *et al.* 1989; Kingsland *et al* 1991; Tan *et al.* 1992). Waterstone *et al.* (1992) found a nonsignificant decline in fertilization in their F1 (43%) sample compared with that for A1 and A2 (56%), although the fertilization rate of 24% in their F2 sample was significantly less than A1 and A2. In their study it was not possible to precisely quantitate the stage at which the decline in fertilization rate occurred because the first three and second three flushes were examined together.

This study confirms and extends the observation that there is a decline in the fertilization rates of oocytes retrieved with repeated flushing. While there was no difference in the fertilization rates of oocytes collected in the initial and dead space aspirates or in the first flush, the fertilization rates in all three were significantly greater than that obtained in the second flush. Another original observation of the study was the significant decline in viability of oocytes collected in the initial aspirate compared with those from the other samples. Moreover, while the viability of oocytes in the dead space aspirate and first flush were similar, both were significantly higher than that in the second flush. Similarly, the cleavage rates in the first three samples were all higher than that in the second flush. Thus out of a total of 300 embryos generated that were suitable for either transfer or cryopreservation, 44·3% were from the initial aspirate, 34·7% from the dead space aspirate, 16·3% from the first flush and only 1·3% from the second flush. Moreover, there were no pregnancies generated in cycles where embryos originating from F2, or only embryos from F1 were transferred. In 10 of the 27 pregnancy cycles, however, embryos from F1 were transferred together with embryos derived from the aspirate (A1 and A2). It is obviously not possible to determine which of the embroyos implanted.

The results of the present study supports previous observations that, provided aspiration is carefully performed, the proportion of oocytes collected at flushing is very small. We are in the process of establishing a transport IVF service in which oocyte retrieval will be performed at external sites without the benefit of embryological services. It is therefore important to have a technique which will enable the retrieval of adequate numbers of good quality oocytes. We have found that the best oocytes are obtained in the initial aspirate plus the 2 ml dead space from the collecting system together with the first 2 ml flush. It is practical to collect A2 and F1 in the same 10 ml test tube. Only oocytes from the aspirate and possibly first flush result in pregnancies. We therefore conclude that by collecting the aspirate with a 4 ml flush (i.e. A2 + F1) oocyte retrieval time is suitably short whilst recovery rates and IVF outcomes are optimized.

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REPRODUCTIVE SCIENCE

Maternal and fetal atrial natriuretic peptide levels at delivery from normal and growth retarded pregnancies

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ABSTRACT

Objective To determine whether circulating fetal levels of the vasodilator atrial natriuretic peptide (ANP) are reduced in pregnancies complicated by intrauterine growth retardation (IUGR).

Design Prospective observational study.

Setting University teaching hospital and research laboratory.

Subjects 25 normal singleton pregnancies delivered at term by spontaneous vertex delivery ($n = 16$) or by elective caesarean section ($n = 9$), and a series of 14 singleton pregnancies complicated by IUGR.

Intervention Measurement of ANP by radio-immunoassay in maternal venous, umbilical artery, and umbilical vein plasma from a series of normal, and IUGR pregnancies.

Main outcome measures Comparison of plasma ANP levels between the three groups; relation between fetal ANP, $P\text{O}_2$ and pH.

Results Mode of delivery did not influence either maternal, umbilical artery or umbilical vein plasma ANP levels in normal term singleton pregnancies. Umbilical vein ANP levels were significantly higher in the IUGR group when compared with normal pregnancies at term (mean 66 95%, CI 36–122 *vs* mean 37, 95% CI 29–47 pg/ml, $P = 0{\cdot}03$) and were inversely related to umbilical artery pH ($R^2 = 65\%$; $P = 0{\cdot}003$).

Conclusions These data suggest that umbilical vein ANP levels are elevated in pregnancies complicated by IUGR, and rise appropriately in response to the stress of acidosis. In the absence of any receptor or second messenger defect within fetoplacental vascular smooth muscle, these data suggest that ANP is not directly implicated in the vascular pathophysiology of IUGR.

Atrial natriuretic peptide (ANP) has vasodilator, natriuretic and diuretic actions, and there are several preliminary reports of its presence in the fetoplacental circulation (Yamaji *et al.* 1986; Robillard & Weiner 1988; Kingdom *et al.* 1989; Panos *et al.* 1989; Fisk *et al.* 1990). The source of this peptide within the fetoplacental circulation is assumed to be the fetal heart (Wharton *et al.* 1988; Gardner *et al.* 1989), and intravascular transfusion therapy (for severe red cell isoimmunisation) has been shown to elevate circulating levels of this peptide, presumably in response to the fluid load (Kingdom *et al.* 1991a).

The exact physiological role of ANP in the fetus remains uncertain, but it may influence vascular impedance within the fetoplacental circulation. Some evidence for this comes from *in-vitro* studies demonstrating both the presence of receptors in the placenta (Sen 1986; Hatjis & Grogan 1988), and an ability of physiological levels of ANP to counteract the vasoconstrictor effect of angiotensin II (McQueen *et al.* 1990a). It is also possible that the increased levels of ANP observed following intravascular transfusion may modify fetoplacental vascular resistance (Kingdom *et al.* 1991a).

The normally low fetoplacental vascular impedance increases in a proportion of pregnancies complicated by intrauterine growth retardation (IUGR), particularly when abnormal Doppler flow velocity waveform patterns have been demonstrated from the umbilical artery (Giles, Trudinger & Baird 1985; McCowan, Mullen & Ritchie 1987; Fok *et al.* 1990). A possible explanation for this increase in vascular impedance is an inadequate ANP-mediated vasodilatation of the fetoplacental circulation, due either to low levels of circulating ANP or to an abnormality of vascular receptor function (McQueen *et al.* 1990b). This paper addresses the former possibility by measuring the plasma levels of ANP at delivery in both normal and growth-retarded babies.

Subjects and methods

Three groups of singleton pregnancies were studied; babies of normal size born at term either by spontaneous vertex

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Table 1. Clinical details of the 14 pregnancies complicated by intrauterine growth retardation (IUGR).

			Birthweight		Prenatal	Umbilical artery		
Subject	Mode of delivery	Gestation at delivery (weeks)	(g)	Centile	diagnosis of IUGR	pH	PO_2	PCO_2
1	F	36	2380	10th	Yes	–	–	–
2	EC/S	41	2690	<3rd	No	7·28	17	36
3	V	38	2350	<5th	No	7·24	15	31
4	SVD	39	2420	<3rd	Yes	7·29	17	33
5	V	40	2770	<5th	No	7·24	14	36
6	PC/S	33**	1660	10th	Yes*	7·28	16	53
7	EC/S	39	2520	<3rd	No	7·14	10	42
8	V	38	2030	<3rd	Yes	7·17	22	51
9	PC/S	38	2420	<3rd	Yes	7.33	26	16
10	PC/S	29**	890	<5th	Yes	7·01	–	32
11	PC/S	29**	560	<3rd	Yes	7·14	23	31
12	PC/S	28**	660	<3rd	Yes	7·23	16	49
13	PC/S	34	1020	<3rd	Yes	–	–	–
14	PC/S	29**	1000	10th	Yes	–	–	–

EC/S = emergency caesarean section, PC/S = planned caesarean section, F = forceps, SVD = spontaneous vaginal delivery, V = ventouse, *indicates one case with absent Doppler end-diastolic flow velocity in the umbilical artery, **indicates cases complicated by pre-eclampsia.

delivery following spontaneous onset of labour (SVD group: n=16), or by elective caesarean section for either breech presentation or a diagnosis of cephalopelvic disproportion in a previous pregnancy (C/S group; n=9), and a series of pregnancies complicated by IUGR (n=14). Gestational age was accurately known in each woman by ultrasound examination performed before 16 weeks' gestation. All the pregnancies resulting in normal size babies were uncomplicated with birthweights ≥25th centile for gestational age (Forbes & Smalls 1982), and 1 and 5 minute Apgar scores ≥8 in each case. IUGR was defined as either birthweight <5th centile for gestational age, or up to the 10th centile when serial ultrasound measurements showed a combination of impaired fetal growth and reduced amniotic fluid volume. Pre-eclampsia was defined as a sustained elevation in blood pressure (>15 mmHg diastolic) to above 140/90 mmHg, accompanied by both proteinuria (>0·3g/24 h) and the development of symptoms necessitating delivery in the maternal interest. The clinical details of the 14 pregnancies complicated by IUGR are summarised in Table 1.

Collection of blood samples

At delivery a long section of umbilical cord was double-clamped, and 5 ml samples of artery and vein blood were collected separately into chilled tubes containing both ethylenediaminetetra-acetic acid (EDTA) and Trasylol (aprotinin-50 KIU/ml blood). A 5 ml sample of maternal peripheral venous blood was collected into similar tubes at the same time. All three samples were immediately centrifuged within the delivery suite at 1000 *g* for 10 min at 4°C, separated and frozen at −20°C. An additional 1 ml sample of umbilical artery blood was collected into a syringe containing 0·1 ml heparin (1000 IU/ml) for automated measurement of pH, $P\mathrm{o}_2$ and $P\mathrm{co}_2$.

Table 2. Atrial natriuretic peptide concentrations in maternal and cord blood in the three study groups.

	Atrial natriuretic peptide (pg/ml)		
	Normal size babies		
Sample site	SVD	C/S	IUGR
Maternal vein	41 (29–60)	57 (26–126)	49 (23–106)
Umbilical vein	35 (26–48)	39 (24–63)	66 (36–122)
Umbilical artery	50 (33–77)	56 (24–127)	83 (39–177)

SVD = spontaneous vaginal delivery; C/S = caesarean section; IUGR = intrauterine growth retardation. Results are means (95% confidence intervals).

Assay for atrial natriuretic peptide

The radio-immunoassay method used (Richards *et al.* 1987) involved the pre-extraction of plasma samples (0·5–1·0 ml); the recovery of ANP during this step was checked by the addition of ^{125}I-labelled ANP to control plasma and found to be >85% in each batch. The dried extracts were reconstituted in buffer, and ANP determined in duplicate by radio-immunoassay. The lower limit of detection of this assay was 3 pg/ml.

Statistical analysis

The ANP data were approximated to a normal distribution using $\log_{(e)}$ transformation as described previously (Kingdom *et al.* 1991a). The results are described as mean and 95% confidence interval (CI) obtained by antilogarithmic transformation of values derived on the $\log_{(e)}$ scale. Comparisons were made using two-tailed Student's t-tests as appropriate, with P values <0·05 being considered significant. Associations between continuous variables were examined by multiple regression analysis methods.

Results

Relation between maternal and umbilical cord plasma ANP

The mean and 95% CI for ANP (expressed in pg/ml) in maternal venous, umbilical artery and vein plasma for each of the three groups are summarised in Table 2. There was no significant difference between maternal and fetal ANP levels within any of the three groups. There was a weak positive relation between maternal and umbilical vein ANP levels in the IUGR group ($R^2 = 30\%$; $P = 0{\cdot}08$), though no such relation was present in the other two groups.

There was a significant positive relation between umbilical artery and umbilical vein ANP levels in each of the three study groups (normal size; vaginal delivery: $R^2 = 36\%$, $P = 0{\cdot}019$; caesarean section: $R^2 = 82\%$, $P = 0{\cdot}005$; IUGR group $R^2 = 76\%$, $P = 0{\cdot}005$). ANP tended to be higher in artery than in vein plasma samples (vaginal delivery $P = 0{\cdot}07$; caesarean section $P = 0{\cdot}09$; IUGR $P = 0{\cdot}07$).

Effect of mode of delivery on plasma ANP levels

There were no significant differences between the two modes of delivery in the normal size groups either for maternal venous, umbilical artery or umbilical vein plasma levels of ANP (Student's *t*-tests; $P \geqslant 0{\cdot}36$ for all comparisons).

Effect of IUGR on umbilical plasma ANP levels

When compared with the combined data from the two normal sized groups, plasma ANP levels in the IUGR group were significantly elevated in umbilical vein plasma ($P = 0{\cdot}03$), but not in either umbilical artery ($P = 0{\cdot}17$) or maternal venous ($P = 0{\cdot}87$) plasma. Figure 1 shows the comparison for umbilical vein plasma; within the IUGR group those first pregnancies complicated by pre-eclampsia tended to have higher values than the other normotensive pregnancies (mean 150 pg/ml *vs* 89 pg/ml), though this difference was not statistically significant.

A multiple regression analysis was used to determine the relative influence of pH, gestational age and Po_2 on $\log_{(e)}$ umbilical vein plasma ANP within the IUGR group. A significant inverse trend was observed between umbilical vein plasma ANP and pH, as shown in Fig 2 ($R^2 = 65\%$; $P = 0{\cdot}003$); though neither Po_2 nor gestational age showed any independent relation with ANP.

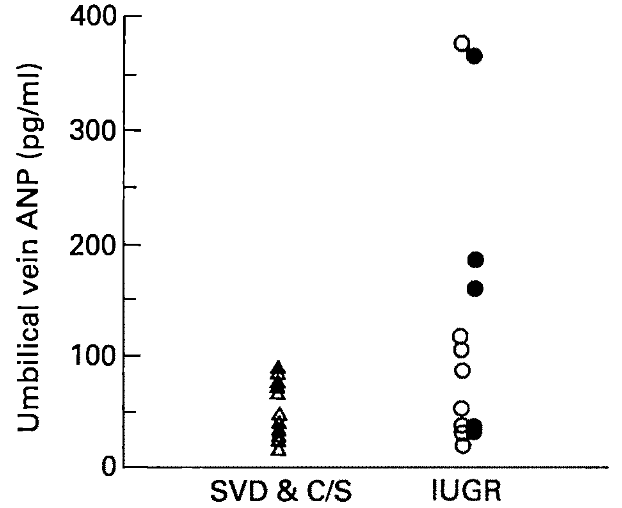

Fig. 1. Comparison of umbilical vein plasma ANP between normal term pregnancies (SVD and C/S groups combined) and the IUGR group. Within the IUGR group, the closed circles indicate the pregnancies which were in addition complicated by pre-eclampsia.

Discussion

The presence of ANP in umbilical cord blood has been described by several groups (Yamaji *et al.* 1986; Ito *et al.* 1988; Castro *et al.* 1989; Voto, Hetmanski & Broughton-Pipkin 1990; Datta *et al.* 1991), indicating higher fetal than maternal levels of this peptide, and a fetal arteriovenous gradient across the placenta. Our data suggest that amongst normal term deliveries, umbilical artery and vein plasma levels of ANP are not influenced by mode of delivery. This confirms the earlier observations of Castro *et al.* (1989), but is in contrast to Voto *et al.* (1990). The latter study reported elevated umbilical artery ANP levels after spontaneous vaginal delivery, but included infants with low 1 min Apgar scores. Since both fetal acidosis and birth stress are associated with large increases in fetal ANP (Castro *et al.* 1989; Andersson *et al.* 1990), this factor may account for the discrepancy between these studies.

Umbilical vein ANP levels were found to be elevated in pregnancies complicated by IUGR which appeared to be related to the development of fetal acidosis. This response by the IUGR fetus may be viewed as a possible adaptive mechanism to promote fetoplacental blood flow since ANP dilates the human fetoplacental vasculature *in vitro* (McQueen *et al.* 1990a).

It is of interest that fetal hypoxia was associated with elevated fetal levels of ANP in a sheep model, though the animals subsequently became acidotic (Cheung & Brace 1988). The closer relation in our IUGR pregnancies between fetal ANP data and pH rather than between Po_2 is not inconsistent with these observations since by contrast IUGR is a chronic condition in which changes in both Po_2 and pH become closely linked. Under such circumstances the release of fetal ANP may, like catecholamine release (Padbury *et al.*, 1982; Weiner & Robillard, 1988), be viewed as part of the normal fetal response to stress.

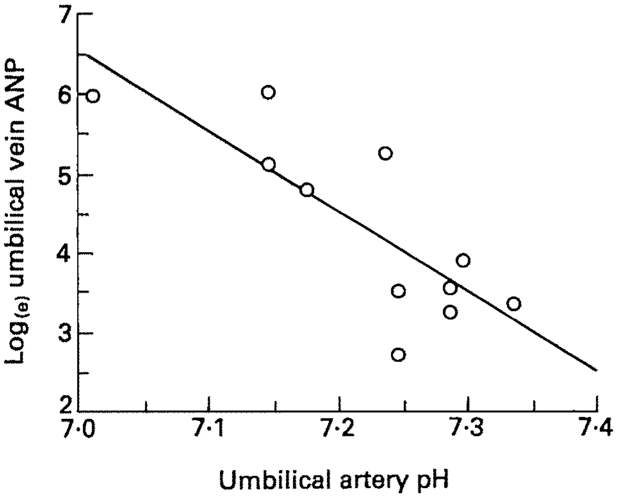

Fig. 2. Relation between umbilical artery pH and umbilical vein plasma ANP in the IUGR group

The earliest gestation at delivery of pregnancies complicated by IUGR introduces the important, potentially confounding, variable of gestational age. However, two studies of fetal ANP, using samples of blood obtained by cordocentesis, showed no independent relation between circulating ANP and gestational age (Weiner & Robillard 1988; Kingdom *et al.* 1991a). Furthermore, in the present study, the two preterm infants with birthweights ≥25th centile born spontaneously at 27 and 32 weeks demonstrated ANP values of 20 pg/ml and 47 pg/ml respectively, which were also comparable with term values—again suggesting that gestational age is not likely to be an important determinant of fetal ANP levels.

No previous study has demonstrated elevated umbilical plasma ANP levels in pregnancies complicated by IUGR. though this has been shown in pregnancies complicated by pre-eclampsia (Castro *et al.* 1989—mean umbilical artery level 150 pg/ml; Hatjis *et al.* 1989—mean 198 *vs* 118 pg/ml in control subjects at term). The possibility of co-existent IUGR was, however, not mentioned in either of these studies, though it is quite possible that acidosis and/or hypoxia is a common factor which explains the elevation in fetal ANP observed in either pre-eclampsia or IUGR. Indeed in the present study, three of the five babies with IUGR associated with pre-eclampsia were acidotic at birth (pH<7·25), and had elevated levels of umbilical vein plasma ANP (Fig. 1).

These data suggest that fetal levels of ANP are appropriate in pregnancies complicated by IUGR. However, these observations do not exclude the possibility that ANP-mediated vasodilatation is impaired within the placenta. The possibility of defects in placental ANP receptor function in pregnancies complicated by either pre-eclampsia or IUGR remains a controversial issue; a preliminary communication from our laboratory suggested a reduction in vascular binding sites for ANP in placentas of pregnancies complicated by IUGR (McQueen *et al.* 1990b), and another group has suggested both an increase in receptor affinity (Hatjis & Grogan 1989) and a decrease in production of the second messenger cyclic guanosine monophosphate (cGMP) in response to ANP (Hatjis & Bottoms 1989) in placentas from women with pre-eclampsia, suggesting that despite normal circulating levels of this peptide, the biological response to ANP (production of cGMP within arteriolar smooth muscle) may be impaired.

Molecular cloning techniques have now characterised both functional (Chinkers *et al.* 1989) and silent, or 'clearance' (Porter *et al.* 1989) receptor subtypes for ANP, providing the opportunity to study placental ANP receptor function in more detail. Preliminary data from our laboratory suggest that expression of the functional ANP receptor subtype is normal in pregnancies complicated by IUGR (Kingdom *et al.* 1991b). Clearly further detailed studies on the effects of ANP on the fetoplacental vasculature in these abnormal pregnancies are indicated, but it seems reasonable to conclude for the present that this placental vasodilator mechanism remains intact in pregnancies complicated by IUGR.

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2 Longterm Safety -breast cancer?

Whilst there is suggestive evidence of a small increased risk of breast cancer with longterm HRT (greater than 5 years), this varies with the type and dose of oestrogen used However, a comprehensive literature review of 30 studies, most of which related to Premarin, concluded that there is evidence that menopausal therapy consisting of 0.625 mg/day of conjugated oestrogens does not increase the risk of breast cancer[1] There are insufficient data to arrive at similar conclusions for any other regimen It is not known whether concurrent progestogen use influences the risk of breast cancer in postmenopausal women taking Hormone Replacement Therapy

3 Prophylaxis of osteoporosis

A minimum daily dose of 0.625 mg Premarin preserves bone mass, thereby reducing the risk of hip fractures by up to 66%[2,3] Further estimates suggest that following 10 years of Premarin therapy, the risk of mortality linked to osteoporosis is reduced by 60%.[4]

4 Reducing cardiovascular disease risks

Premarin – A recent review of considerable epidemiological evidence has shown a 50% reduction in risk of coronary disease in oestrogen users.[5] Conjugated oestrogens, ie: Premarin, were the most common form of oestrogens used in all these studies

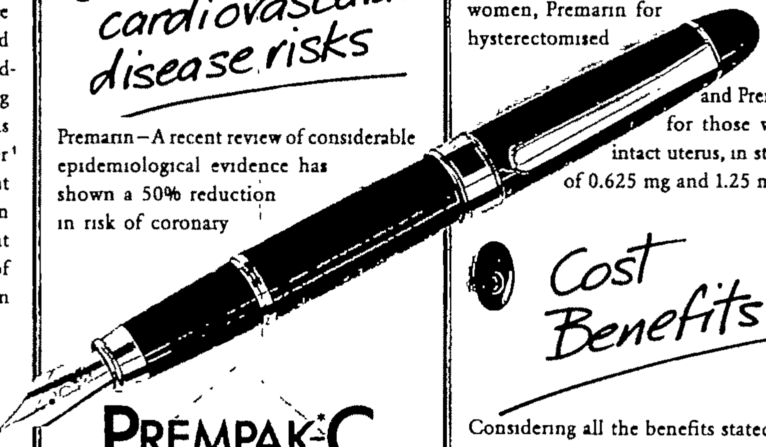
Prempak-C – A possible attenuation of these effects may occur with the addition of a progestogen. However, epidemiological data on combined oestrogen and progestogen are limited.

5 Versatile and Immediate Treatment

Premarin and Prempak-C can both be prescribed at the onset of the earliest menopausal symptoms and are suitable for the vast majority of menopausal women, Premarin for hysterectomised women and Prempak-C for those with an intact uterus, in strengths of 0.625 mg and 1.25 mg

6 Cost Benefits

Considering all the benefits stated above, Premarin at £22.08 and Prempak-C at £48.64 (12 months' therapy) seems a very small price to pay[6]



PREMPAK-C
(Conjugated Oestrogens + Norgestrel)

PREMARIN
(Conjugated Oestrogens)

ABBREVIATED PRESCRIBING INFORMATION

PREMARIN **USES** Menopausal and postmenopausal oestrogen therapy in women without a uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures
DOSAGE AND ADMINISTRATION Natural conjugated oestrogens 0 625mg – 1 25mg daily. Continuous administration is recommended In women with an intact uterus the addition of a progestogen for 10 12 days per cycle is essential
CONTRA-INDICATIONS Known or suspected pregnancy and during lactation History of known or suspected cancer of the breast Oestrogen dependent neoplasia Undiagnosed abnormal genital bleeding Active thrombophlebitis or thromboembolic disorders Acute or chronic liver disease Rotor or Dubin-Johnson syndrome Severe cardiac or renal disease
WARNINGS AND PRECAUTIONS Some studies have reported a small increased risk of breast cancer in longterm oestrogen replacement therapy users (greater than 5 years), others however have not shown this relationship It is not known whether concurrent progestogen influences this risk The risk of endometrial hyperplasia and carcinoma with unopposed oestrogen use is lowered by the addition of a progestogen Diseases that may deteriorate during therapy include otosclerosis multiple sclerosis, systemic lupus erythematosis, porphyria, melanoma, epilepsy, migraine and asthma Use with caution in patients with pre-existing uterine fibroids, endometriosis, breast nodules, fibrocystic disease, and in those with a history of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, cardiac or renal dysfunction Discontinue if jaundice, migraine, visual disturbances, thromboembolic phenomena or significant hypertension develop Certain endocrine and liver function tests may be affected Rarely idiosyncratic hypertension may occur Discontinue treatment prior to surgery or prolonged immobilisation Gallbladder disease. Insulin requirements may be altered Premarin is not an oral contraceptive
SIDE EFFECTS The following have been reported with oestrogen therapy premenstrual-like syndrome, increase in size of uterine fibromyomata, vaginal candidiasis, changes in cervical erosion and secretion, cystitis-like syndrome, breast changes, gastrointestinal symptoms, chloasma melasma, erythema multiforme, erythema nodosum, haemorrhagic eruption, alopecia, hirsutism steepening of corneal curvature, intolerance to contact lenses, headaches, migraine, dizziness, mental depression, chorea, weight changes, reduced carbohydrate tolerance, aggravation of porphyria, oedema, changes in libido, leg cramps
FURTHER INFORMATION Oral conjugated equine oestrogens have been shown to increase HDL and decrease LDL cholesterol levels thus improving the lipid profile, a recognised factor contributing to the beneficial effect of conjugated oestrogens on the risk of coronary heart disease in postmenopausal women
PRODUCT LICENCE NUMBERS Premarin 0 625mg PL0011/0165 Premarin 1 25mg PL0011/0166 Premarin 2 5mg PL0011/0167
BASIC NHS PRICE Premarin 0 625mg £1 84 (28 days) For full prescribing information please refer to data sheet

PREMPAK-C **USES** Menopausal and postmenopausal oestrogen therapy for women with an intact uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures
DOSAGE AND ADMINISTRATION. Natural conjugated oestrogens 0 625mg – 1 25mg daily and one norgestrel 0 15mg tablet should be taken daily from day 17 to day 28 of oestrogen therapy
CONTRA-INDICATIONS As for Premarin
WARNINGS AND PRECAUTIONS As for Premarin Prempak-C is not an oral contraceptive
SIDE EFFECTS· As for Premarin Breakthrough bleeding and spotting Change in menstrual flow, dysmenorrhoea, amenorrnoea
FURTHER INFORMATION As for Premarin Possible attenuation of these effects on lipids may occur with the addition of a progestogen
PRODUCT LICENCE NUMBERS Prempak-C 0 625mg PL0011/0161 Prempak-C 1 25mg PL0011/0162
BASIC NHS PRICE £4 06 (28 days) For full prescribing information please refer to data sheet
REFERENCES 1 Dupont W D and Page D L (1991) Arch. Int Med 151, 67-72 2 Lindsay R et al (1984) Obstet Gynecol 63, 759-763 3 Kiel D P et al (1987) NEJM, 317, 1169-1174 4 Ross R K et al (1989) Lancet, 1 505 5 Stampfer M J and Colditz G A (1991) Prev Med, 20, 47 63 6 MIMs November 1992

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CASE REPORTS

Raynaud's phenomenon and peripheral gangrene complicating scleroderma in pregnancy—diagnosis and management

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Case report

A 20-year-old previously healthy woman of caucasian origin developed Raynaud's phenomenon of the distal phalanges of her right hand during the first trimester of her first spontaneous pregnancy. On examination, her heart, chest, lungs, optic fundi and neurological system were normal. Laboratory studies revealed a normal blood count and coagulation screen and no evidence of cryoglobulins or cold agglutinins. Creatinine clearance was 101 ml/min, without proteinuria. the erythrocyte sedimentation rate was increased to 75 mm in the first hour. Albumin/globulin ratio was lower than the normal expected levels in pregnancy. Antinuclear antibody titre was 1:40 with typical fluorescence pattern of fine speckles.

Consequently, based on the typical antinuclear antibody titre and the elevated globulins level, we had assumed that this Raynaud's phenomenon was the first symptom of the immune-mediated disease—scleroderma. Her antenatal follow-up was uncomplicated until the 32nd week of gestation when she developed severe intractable pain, cutaneous ulcers and gangrene of the distal second, third and fourth phalanges of her right hand (Fig. 1).

A trial of treatment, with high doses of methyldopa, dipyridamole and nifedipine yielded only a slight improvement. With the continuing aggravation of the symptoms, she received repeated multiple stellate ganglion blocks with 50 mg of bupivacaine HCl 0·5%, until complicated by the appearance of Horner's syndrome. To protect her severely ulcerated digits from deep infection and osteomyelitis, she had frequent iodine soaks, gentle local debridement and prophylactic broad spectrum antibiotics. The deterioration of her renal function to a creatine clearance of 46 ml/min with moderate proteinuria and the threatening need for amputation of her fingertips necessitated induction of labour at 37 weeks. Vaginal PGE_2 tablets were introduced, resulting in precipitate labour and spontaneous birth of a female newborn weighing 2980 g in good condition. A continuous epidural block with bupivacaine was used during labour.

The postpartum period was uneventful, with a dramatic improvement of the digital ischaemic lesions and her creatinine clearance returned to 118 ml/min without proteinuria. An intrauterine device was inserted at six weeks postpartum.

Discussion

Raynaud's phenomenon may antedate other evidence of scleroderma by many years (Mor-Yosef *et al.* 1984; Maymon & Fejgin 1989; Steen *et al.* 1989). Patients with such paroxysmal vasospasm have a persistently subnormal capillary blood flow of the fingers and in some cases even persistent intimal and adventitial fibrosis without evidence of inflammation (Rodnan *et al.* 1980). Capillary changes may be an early predictor of evolution to scleroderma in individuals who clinically appear to have only Raynaud's phenomenon (Furey *et al.* 1975). Small areas of ischaemic necrosis or ulceration of the fingertip, leaving pitted scars, are frequent and in some patients gangrene of the terminal position of the distal phalanx ensues. Those with early, rapidly progressive, diffuse skin thickening are at higher risk of developing renal crisis (Steen *et al.* 1989).

Women are affected approximately three times more often than men, especially in the childbearing years. The combination of scleroderma and pregnancy is very rare, probably because the disease is associated with decreased fertility

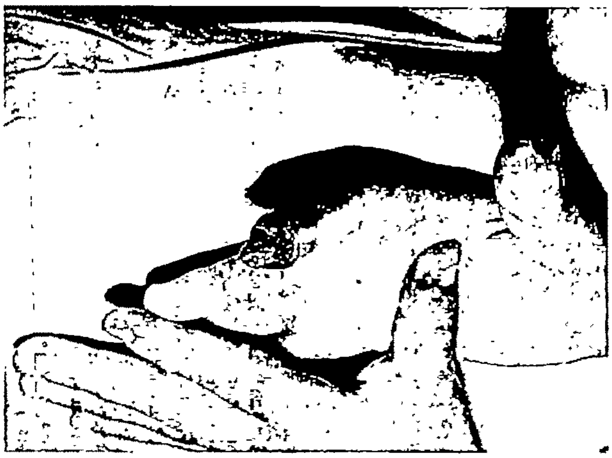

Fig. 1. Gangrene of the distal phalanges of right arm—Raynaud's phenomenon in pregnancy.

Correspondence: Dr Ori M. Avrech

(Mor-Yosef *et al.* 1984; Maymon & Fejgin 1989; Steen *et al.* 1989; Spellacy 1964; Ballow *et al.* 1984). Of the approximately 150 cases of scleroderma in pregnancy reported in the literature, one third were aggravated during pregnancy and 15% died from pregnancy related complications. We found only one report of scleroderma in pregnancy complicated by gangrene of the extremities (Smith & Pinals 1982) necessitating emergency amputation of both legs, distal arm and four fingers of the other hand. The case was earlier complicated by retained placenta, sepsis, DIC, renal failure and shock which may have contributed to the postpartum development of the severe ischaemic lesions. The present case is the first report of the onset of severe Raynaud's phenomenon during pregnancy and its deterioration to digital gangrene, as a first and a single sign of scleroderma. Several drugs which are relatively contraindicated in pregnancy were proposed for treatment, such as ketanserin, d-penicillamine (Lyle 1978), and captopril (Baethge & Wolf 1989). Corticosteroids (Hoffman & Diamond 1961) and colchicine (Guttadauria *et al.* 1977) are not contraindicated in pregnancy but were not sufficiently effective.

The vasodilatating drugs seem to be more promising: reserpine, alpha-receptor blocking and beta receptor stimulating drugs, PGE_1, methyldopa, dipyridamole and lately calcium channel blockers such as nifedipine (Rodeheffer *et al.* 1983; Smith & McKendry 1982; Vayssairat 1989). This drug can also be safely administered during pregnancy (Wilson & Kirby 1990). Surgical or chemical thoracic sympathectomy (Blunt & Porter 1981) were followed by partial and usually transient improvement in the Raynaud's phenomenon without a significant or sustained influence on the course of the cutaneous changes. Supporting measures have a prominent role in therapy, but deeper infections must be treated more radically with excision of infected tissue and at times even by amputation. Pregnancy should be terminated when typical visceral complications develop that could be life threatening or when the gangrenotic process is progressive and even resistant to radical therapy. A short induction–delivery interval may be expected and related to the biochemical changes occurring in the connective tissue in this disease.

An epidural block is the preferred method of anaesthesia for both vaginal and abdominal delivery, especially since peripheral vasodilatation relieves the symptoms of the Raynaud's phenomena (Thompson & Conklin 1983; Younker & Harrison 1985). In the presented case we believe, that it was the nifedipine given three times daily and the repeated stellate ganglion bupivacaine blocks coupled with the meticulous local supportive treatment of the fingers that allowed the continuation of pregnancy until 37 weeks of gestation when further deterioration necessitated induction of labour.

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Magnetic resonance imaging pelvimetry: a useful adjunct in the management of the obese patient

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Case report

This obese patient weighed 101kg; she had a rare autosomal dominant form of endosteal hyperostosis, but no other significant past medical history. Her first pregnancy had proceeded uneventfully until 34 weeks of gestation when she developed mild hypertension. On admission, her blood pressure was 135/100 mmHg, the uterine size was compatible with dates and fetal presentation cephalic. There was no significant proteinuria and her haematological and biochemical parameters were unremarkable. Her blood pressure remained stable with conservative management and induction of labour was performed at term. A lower segment caesarean section became necessary because she failed to progress beyond 3cm cervical dilatation some thirteen hours after artificial rupture of membranes and commencement of intravenous syntocinon. It was uncertain whether the reason for this failure to progress was cephalopelvic disproportion (CPD) or uterine dysfunction for abdominal and vaginal examination were hampered by the patient's obesity At caesarean section (carried out with some difficulty due to the patient's size), at least three-fifths of the fetal head was palpable abdominally.

Post-partum pelvimetry was requested but proved technically difficult; a satisfactory lateral radiograph of the pelvis could not be obtained due to the size of the patient. The AP pelvic radiograph was of poor quality, but the transverse inlet measurement was obtained (12·8cm). However, the bispinous distance could not be measured for the spines were too indistinct. A digital lateral radiograph from a CT scanner was attempted, but again the x-ray tube output was insufficient for satisfactory results while a x-ray fluoroscopy was similarly ineffective. Conventional radiography was thus unable to give definitive pelvic measurements in this obese patient.

The woman became pregnant again. At booking, her weight was again 101kg and the antenatal course was uneventful apart from recurrent episodes of abdominal pain and labile blood pressure towards term. There was some uncertainty over the appropriate management of the delivery in view of the lack of satisfactory pelvimetry. Magnetic resonance imaging (MRI) pelvimetry was therefore carried out and good quality scans were obtained showing all the relevant pelvic measurements (Figs. 1–3). Pelvic size was clearly shown to be adequate. The patient was managed accordingly and achieved a normal vaginal delivery at term.

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Discussion

Pelvimetry may sometimes be useful in the management of term pregnancy. Its most common indication today is as part of the overall assessment of a breech pregnancy where vaginal delivery is planned (Collea *et al.* 1980; Gimovsky *et al.* 1983). The two methods most commonly used are conventional radiography and computed tomography (CT) pelvimetry.

Conventional x-ray pelvimetry uses standard AP and lateral radiographs from which measurements are made directly. Concern over the potentially carcinogenic effects on children of irradiation *in utero* has led to a more critical use of this technique, although evidence suggests that it is still over-employed (Mole 1990). Various technical improvements, including gridless radiography with fast film-screen combinations and strict collimation, have led to a relative reduction in overall dose (Russell *et al.* 1980). The technique is somewhat inaccurate (Lundh *et al.* 1986).

Computed tomography pelvimetry uses the digital scout

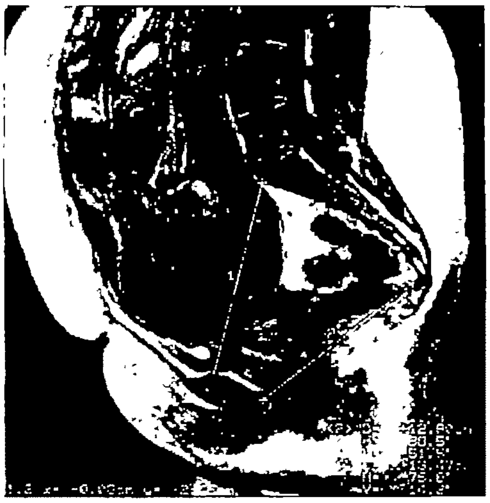

Fig 1. Median sagittal gradient-echo pelvimetry image. This is used to measure the sagittal inlet and outlet as shown. Other elements of fetal and maternal anatomy are also displayed.

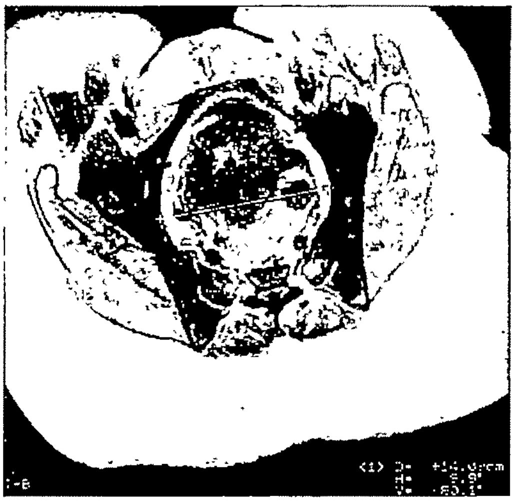

Fig. 2. These oblique axial scans are taken in the plane of the pelvic inlet They allow measurement of the transverse inlet and assessment of its overall shape.

views from a CT scanner for the pelvic measurements, usually with an additional axial slice for the bispinous distance (Federle *et al.* 1982; Suramo *et al.* 1984; Adam *et al.* 1985). Dose is less than with conventional x-ray pelvimetry, although further axial slices may sometimes be necessary to localise the ischial spines, and this will increase the radiation dose significantly (Moore & Shearer 1989; Aronson & Kier 1991). Use of correction formulae or careful positioning of the patient with respect to the plane of the centre of rotation of the scanner is needed for accuracy of the transverse measurements (Weisen *et al.* 1991).

All x-ray-based pelvimetry techniques are subject to an increased error with the obese patient. Reduced contrast due to x-ray scatter leads to poor visualisation of bony landmarks while difficulty with patient positioning will increase geometric error. In the above case, only the transverse inlet measurement could be made using these techniques, and no useful information was obtained about the other dimensions.

Obese patients are well imaged by MRI pelvimetry which allows good depiction of bony and soft-tissue landmarks (Stark *et al.* 1985). No ionising radiation is used, and there are no known hazards to mother or fetus from the static, gradient or radiofrequency fields employed in current clinical imaging scanners (National Radiological Protection Board 1991). Our technique of MRI pelvimetry uses gradient-echo fast-scans which can produce all the relevant images for measurement in less than five minutes of scanning time. Measurements are highly accurate in all planes, and easily performed due to the inherent high tissue-contrast. In addition, assessment of the shape of the pelvic inlet can be made (Fig. 2). The technique has been described in full elsewhere (Wright *et al.* 1992).

In conclusion, where pelvimetry is indicated in the obese patient, MRI can easily and quickly provide a high quality examination without the use of ionising radiation. It may, therefore, contribute to the overall assessment of these difficult patients and allow clinical judgments to be made with a greater degree of confidence.

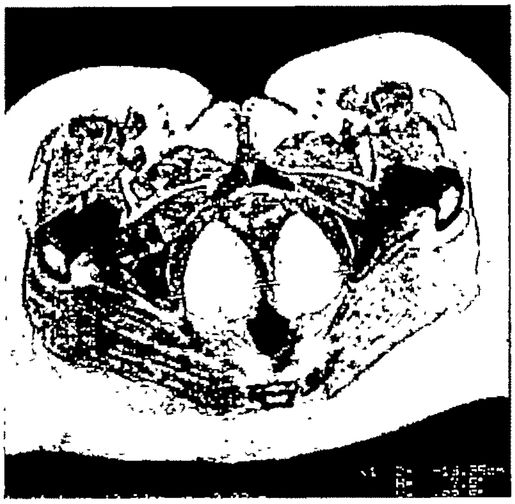

Fig. 3. Further oblique axial scans allow easy measurement of the bispinous distance in the mid-pelvis.

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Recurrent idiopathic non-immunologic hydrops fetalis: a report of two families, with three and two affected siblings

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Case 1

A 28 year-old white woman had four normal pregnancies with healthy children by her first partner. She remarried and subsequently had two mid-trimester miscarriages about which information was scanty, two normal deliveries and then three pregnancies affected with hydrops fetalis (Table 1). The three affected fetuses developed ultrasonographic evidence of worsening pericardial effusion, pulmonary effusion and ascites in the second trimester. Echocardiography performed on the last two affected fetuses showed markedly dilated cardiac chambers with apparently normal myometrial function. Postmortem examination confirmed the hydrops but otherwise the fetal anatomy was normal. Both her partners were white and there was no consanguinity. The mother's blood group was A Rhesus positive without irregular antibodies, glucose tolerance was normal and serological tests for syphilis, viral studies (cytomegalovirus, rubella), toxoplasmosis and lupus anticoagulant tests were negative. Fetal blood sampling was not performed in any cases.

Case 2

A 28 year-old white woman had had three children, the last two affected with idiopathic non-immunological hydrops fetalis NIHF (Table 1). There was no history of consanguinity. Her blood group was O Rhesus positive and her husband's A Rhesus positive, both without irregular antibodies. Glucose tolerance test, serological tests for syphilis, viral studies (cytomegalovirus, rubella), toxoplasmosis test and lupus anticoagulant were negative. The first affected child was stillborn at 29 weeks and the second developed ultrasonographic evidence of worsening oedema of the face, scalp and abdomen in the second trimester and was born by caesarean section at 30 weeks. The cord haemoglobin was 14 g/dl, bilirubin was 10 mmol/l, urea of 2·7 mmol/l and sodium of 120 mmol/l, total protein of 28 g/l and albumin of 20 g/l. The fetus died at 6 hours of age. The mother had normal biochemical and haematological indices.

Discussion

Non immunologic hydrops fetalis was first identified as a separate condition by Potter (1943). It is now recognised that it is caused by a large number of pathologically distinct conditions. Nevertheless, in a recent series (Hansmann *et al.* 1989), 12% (47/402) were classified as idiopathic. Siblings affected with the idiopathic form had not been reported until 1979 (Cumming 1979) but subsequent reports (Etches & Lemon 1979; Silverstein & Kanbour 1981; Schwartz *et al.* 1981; Hansmann *et al.* 1989) have raised the possibility that some cases might be caused by a recessive gene. These authors present two further families with recurrent idiopathic hydrops fetalis that lend support to this hypothesis.

While the diagnosis of idiopathic NIHF is made by excluding a variety of possible causes or associations (Etches & Lemons 1979), an autosomal recessive inheritance pattern is suggested by the occurrence of idiopathic NIHF in siblings of a family. The present cases should be distinguished from the only well recognised cause of recurrent non-immune hydrops, homozygous alpha thalassaemia. All the parents of affected fetuses in the present series had normal haemoglobin electrophoresis, and in the second affected fetus in Case 2 the cord haemoglobin was normal. The occurrence in Case 1 of three (or possibly five) hydropic fetuses of different sexes by a second partner after two normal births suggests a recessive aetiology. Etches & Lemon (1979) also reported one family of three affected siblings among 22 cases of non-immune hydrops fetalis, but in their series an abnormality of placentation (placenta membranacea) was common to all fetuses. In the second affected child of Case 2, cord blood at delivery showed hypoproteinaemia. This is similar to one of the cases reported in the series by Hansmann *et al.* (1989) where the only fetus with idiopathic NIHF that survived of the 47 reported followed three siblings each of whom had died of idiopathic NIHF. Fetal blood sampling revealed a very low serum protein level. Fetal therapy with repeated instillation of albumin and blood and direct administration of digoxin and frusemide resulted in the birth of a live baby who survived. Fetal parvovirus 19 infection is another well recognised cause of non-immune hydrops but would not be expected to cause recurrent disease since only primary maternal infection is associated with viraemia.

When NIH is seen by ultrasound, further investigations such as Doppler flow velocity waveform examination, M-mode echocardiography, chorionic villus sampling for

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Table 1. Two families with recurrent NIHF with a total of five siblings

Date of birth	Sex	Gestation (weeks)	Pregnancy complications	Fetal outcome/wt(g)		Pathology
Case 1						
1972	M	40	—	alive/well	2810 g	—
1973	M	36	—	alive/well	2380 g	—
1975	M	40	—	alive/well	2954 g	—
1978	M	40	—	alive/well	3800 g	—
Change of partner						
1981	-	19	miscarriage			
1983	-	26	missed abortion			
1986	M	41	—	alive/well	2981 g	—
1987	M	37	—	alive/well	3090 g	—
1988	F	16	fetal hydrops, induced	oedematous	62 g	placenta oedematous 200 g
1989	M	22	fetal hydrops, induced	oedematous	520 g	placenta oedematous
1990	M	26	fetal hydrops, induced	oedematous	1280 g	placenta oedematous 1420 g
1991	M	40	—	alive/well	3290 g	—
Case 2						
1981	F	40	—	alive/well	2860 g	—
1984	F	29	fetal hydrops, induced	stillbirth	2550 g	—
1987	F	22	fetal hydrops, C/section at 30 weeks	NND		—

karyotype, fetal blood sampling to determine blood biochemistry, liver enzymes, haemoglobin electrophoresis and viral antibody titres may permit specific diagnosis.

If idiopathic NIHF is diagnosed antenatally, there are three management options: firstly, conservative management with observation only; secondly, in view of the poor prognosis, termination of pregnancy in the second trimester; thirdly, intensive antenatal and neonatal treatment. Hansmann *et al.* (1989) have recently reported fetal survival after aggressive antenatal treatment. In general, the prognosis for

Table 2. All published cases of recurrent idiopathic NIHF. NND = neonatal death.

No	Age	Gestation (weeks)	Obstetric history	Fetal outcome and sex	Birth weight
1[a]	—	27	INIHF	Stillbirth/—	—
2[a]	—	27	INIHF	Stillbirth/—	—
3[a]	—	27	INIHF	Stillbirth/—	—
4[a]	—	—	Fetal hypoproteinaemia. Treated with *in utero* albumin, blood, digoxin, frusemide.	Alive/well/—	—
5[b]	24	34	Intermittent hypertension, no proteinuria. Spontaneous ruptured membranes	Early NND/M	4100 g
6[b]	26	36	—	Stillbirth/—	4000 g
7[b]	29	33	Polyhydramnios, hypertension	Stillbirth/M	2340 g
8[b]	30	32	Excessive maternal weight gain (2700 g in 4 days).	NND (56 h)/F	2610 g
9[c]	21	28	Polyhydramnios and pre-eclampsia	Early NND	—
10[c]	23	28	Polyhydramnios and pre-eclampsia	NND (72 h)/M	1800 g
11[d]	—	34	Polyhydramnios. Excessive weight gain	Early NND/—	2800 g
12[d]	—	36	Polyhydramnios	Early NND/—	3910 g
13[e]	26	26	Acute polyhydramnios	Stillbirth/—	1095 g
14[e]	27	34	Acute polyhydramnios Pre-eclampsia Spontaneous labour, fetal distress, caesarean section	Early NND[f]/—	2500 g
15[e]	28	33	Polyhydramnios. Treated with betamethasone. Elective C/section	Alive/well/—	1940 g

[a] Hansmann *et al.* (1989)
[b] Silverstein & Kanbour (1981)
[c] Cumming (1979)
[d] Schwartz *et al.* (1981)
[e] Etches & Lemon (1979)

fetal survival in idiopathic NIHF however appears worse than for other causes of NIHF such as tachyarrhythmia and haematologic disorders (Hansmann *et al.* 1989) with a mortality rate of 50–100% (Etches & Lemon 1979; Schwartz *et al.* 1981). For recurrent idiopathic NIHF the reported mortality including the present series is 18/20 (90%) (Tables 1 and 2).

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Unreactive fetal heart rate pattern and atrial flutter

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Case report

A 34-year-old multiparous woman with an uneventful antenatal history presented in her third pregnancy at 37 weeks' gestation to her local antenatal clinic for confirmation of the onset of labour as she had intended to have a home delivery. A prolonged (60 min) cardiotocograph (CTG) was unreactive; therefore she was referred to the maternity unit for assessment.

Assessment at the maternity unit revealed a fetal heart rate on the CTG of 155 bpm with poor variability and with no reactivity to painful uterine contractions. Echocardiography (M-mode and 2-dimensional) was performed which revealed a structurally normal heart with an atrial rate of 440 beats per minute with variable conduction. Biophysical assessment, excluding CTG, was normal as was the umbilical artery Doppler (pulsatility index (PI) = 0·9). There was no evidence of cardiac enlargement or hydrops. Since she was in early labour she was transferred to the labour ward where amniotomy was performed. Throughout labour the CTG remained unchanged. Fetal surveillance was maintained by performing regular fetal scalp blood samples for pH estimation which were normal. She had a normal vaginal delivery after 3 h of a 3340 g live infant male with good Apgar scores. The infant's baseline fetal heart rate was 150 beats per minutes which increased to 230–240 bpm intermittently; examination of the infant was otherwise normal. An electrocardiographic diagnosis of atrial flutter (rate > 400 bpm) was made with a variable atrioventricular block of 3–1:1. Echocardiography revealed no structural abnormality. The atrial flutter was treated with digoxin and sinus rhythm was established within three days. The infant was discharged six days after commencement of the digoxin (20 μg twice daily) in sinus rhythm which has been maintained during outpatient follow-up.

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Discussion

A diagnosis must always be made when confronted with an unreactive FHR pattern if unnecessary emergency caesarean section is to be avoided. By investigating as summarised in Table 1, the diagnosis can be made rapidly in most cases with the use of a CTG monitor and a ultrasound scan (USS) machine. The commonest cause for an unreactive FHR pattern is when the fetus is in behavioural state F1 (quiescent state), which on average lasts 21 mintues (range 3–38 minutes) (Pillai & James 1990) with a maximum duration of 55 minutes (Nijhuis *et al.* 1982); therefore, the diagnosis can be made by prolonging the CTG for up to 60 minutes. While this is being done a maternal history and examination to exclude maternal thyrotoxicosis or medication effect (benzodiazepines; pethidine) can be done. A drug induced unreactive FHR usually lasts 30–40 minutes without associated decelerations (Martin 1982). Cardiac arrhythmias can be diagnosed if the USS machine has an M-mode facility. If there is no arrhythmia but there is fetal movement with the FHR pattern remaining unreactive, this is suggestive of a neurodevelopmental abnormality in the fetus. However, if the fetus fails a

Table 1. Differential diagnosis and investigation of an unreactive fetal heart rate pattern.

Diagnosis	Investigation and interpretation
Fetal behavioural state 1F	Extend CTG recording to 60 min
Maternal drugs	Extend CTG recording 40 min, no decelerations + history of pethidine/diazepam
Cardiac tachyarrhythmia	Echocardiography: B + M-mode Maternal history/examination/blood tests for thyroid dysfunction
Neurodevelopmental abnormality	Fetal behavioural study will show dissociation
Congenital anomaly	USS of CNS, e.g. anencephaly
Brain death	Biophysical assessment. (BPA) = no fetal movement; fetal blood sampling (FBS)* = normal fetal blood gases
Fetal hypoxia	Abnormal BPA (decelerations with contractions); FBS* = abnormal fetal blood gas

*Cordocentesis/scalp sample if in labour.

biophysical assessment (BPA) after a 60 minute FHR unreactive pattern recording, this is suggestive of fetal brain death; this can be distinguished from fetal distress by there being no FHR decelerations and the presence of normal gases revealed by fetal blood sampling. The FHR in fetal brain death syndrome is always relatively high (Nijhuis *et al.* 1990) in comparison to that of F1.

Management of this case was simplified as the woman was multiparous, in early labour with a favourable cervical/Bishop score, and there was no evidence of fetal hydrops. The problem of how to monitor for fetal distress in labour was overcome by performing regular fetal scalp sampling which was helped by a relatively short labour.

Tachyarrhythmias are the commonest clinically important fetal arrhythmia. The majority (95%) of fetal tachyarrhythmias are due to reciprocating supraventricular tachycardia (RSVT) with atrial flutter (AF) being much less common (Kleinman & Copel 1991*a*). The danger with atrial flutter is the development of cardiac failure (hydrops) and fetal death. In the presence of hydrops fetalis, atrial flutter is more difficult to treat as compared to RSVT (Kleinman & Copel 1991*a*), reflected by a 40–50% perinatal mortality and a high caesarean section rate (60–100%) (Maxwell *et al.* 1988; Hansmann *et al.* 1991). Before considering treatment, it is important to exclude structural cardiac anomalies which can be present in up to 10% (Wladimiroff & Stewart 1985) of cases; these are considered to be more common with atrial flutter and are associated with an extremely poor prognosis with or without vigorous *in-utero* and postnatal therapy (Moller *et al.* 1969; Kleinman & Copel 1991*a*). Other causes to be considered are viral infections (coxsackie B and cytomegalovirus (Wladimiroff & Stewart 1985)) and maternal thyrotoxicosis.

Accurate diagnosis of this type of arrhythmia is important before instituting antiarrhythmic therapy as all antiarrhythmic agents have a potential proarrhythmia effect on the fetus, and/or the mother, especially if given for the wrong arrhythmia. The long term prognosis is different depending on the type of arrhythmia. Whereas no or infrequent recurrences are found with atrial flutter after infancy (Moller *et al.* 1969; Lundberg 1973), a 20% recurrence risk is reported with paroxysmal atrial tachycardia (Lundberg 1973). Digoxin is the first line drug of choice in treating atrial flutter (Allan *et al.* 1991; Kleinman & Copel 1991*b*) with therapy continuing for up to 1 year post delivery. In the case of atrial flutter being diagnosed in the preterm fetus, then maternal administration of digoxin is the first drug of choice.

Long term follow up of all atrial flutter cases is mandatory.

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SHORT COMMUNICATIONS

Determination of twin zygosity by DNA hybridisation to wild type bacteriophage M13

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The incidence of twin pregnancy is about 1% (Registrar General 1979) of which two thirds are dizygotic and one third are monozygotic (Bulmer 1970). Dizygotic twins always have dichorial placentation whilst monozygotic twins may be mono- and dichorial. Antenatal ultrasound can determine zygosity when the twins are of different sex, but it is impossible to identify monozygotic twins with certainty unless they are conjoined. Techniques which may be used to identify monochorial monozygotic twins include counting of the number of layers in the septum dividing the sacs and transfusion of maternal blood into one twin followed by sampling of the other twin for a Kleihauer test to detect communication between the two circulations. Postnatal examination of the placentas and membranes will identify those monozygotic twins who have monochorial placentation but zygosity cannot be determined for same sex twins with dichorial placentation.

Analysis of DNA polymorphisms can separate monozygotic from dizygotic twins with certainty. This can be performed antenatally if fetal blood or chorion villi from separate placentas is available, or postnatally using cord or neonatal blood. Zygosity testing may be of value in the diagnosis of twin-to-twin transfusion syndrome, in exclusion of monozygosity when one twin has a lethal abnormality, or prior to selective fetocide where separate placentas cannot be seen. Zygosity testing is performed probably most frequently at parental request.

Zygosity testing is usually performed using the hypervariable minisatellite DNA probes described by Jeffreys *et al.* (1985). DNA from each twin is digested with a frequent cutter restriction enzyme, Southern blotted and hybridised to the Jeffreys probe. The autoradiograph produced will show a complex banding pattern. Any individual fetus will inherit approximately half of the bands from each parent. Dizygotic twins will share some but not all bands. Monozygotic twins will have an identical banding pattern. Jeffreys probes are only available under licence and their diagnostic use is restricted. However, DNA from bacteriophage M13 will, under certain conditions, detect a distinct set of hypervariable regions in human DNA (Vassart *et al.* 1987). Bacteriophage M13 is used as a vector for DNA sequencing, is available in virtually all molecular biology laboratories, and carries no restrictions upon its use. We have therefore assessed the use of bacteriophage M13 DNA as a tool to determine zygosity in twin pregnancy.

Methods

DNA was obtained, using standard techniques, from cord blood from seven pairs of same-sex twins. DNA (4 μg) was digested with the restriction endonuclease *Taq* I and Southern blotted onto Hybond-N nylon filters. Filters were baked and prehybridized for 2 h at 42°C in 0·9 M sodium chloride, 0·09 M sodium citrate, 5 mM EDTA (pH 8), 0·25% dried skimmed milk (Marvel™).

Wild type bacteriophage M13 DNA was radiolabelled using ^{32}P-labelled dCTP by random hexanucleotide priming.

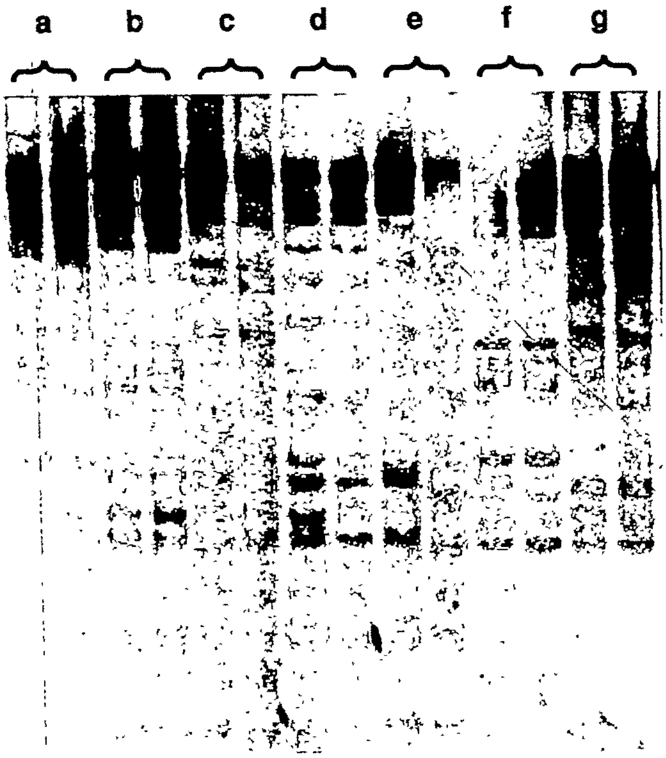

Fig. 1. DNA prepared from each of 7 same-sex twin pairs has been digested with the restriction enzyme *Taq* I, Southern blotted and hybridized to wild type bacteriophage M13 DNA. Analysis of this autoradiograph shows that twin pairs a, b, d, f and g are monozygotic, whilst twin pairs c and e are dizygotic.

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CORRESPONDENCE

Can out-of-hours work by junior doctors in obstetrics be reduced? and role of the senior house officer in the labour ward

Dear Sir,

The conclusion by McKee *et al.* (1992) that there is scope for reducing the workload of junior obstetricians at night through the adoption of an extended role by midwives is thoughtfully commented upon by Pogmore (1992) in the same issue The findings by McKee about epidurals in labour must, however, give rise to concern. He found that in one instance an obstetric SHO commenced epidural anaesthesia and that in two of the four hospitals studied the task of topping-up epidurals was shared between the SHO, the anaesthetist and the midwife (in the other two hospitals no details about this task were available). The training of anaesthetists in obstetric analgesia and anaesthesia is often informal, despite guidelines having been produced by the Royal College Anaesthetists (1991) In general no anaesthetist will be on-call for the labour ward with less than one year of anaesthetic training.

The training of midwives in the management of women with epidurals and topping-up epidurals is also thorough The acceptance by Mr Pogmore that the topping-up of epidurals is all part of the job of the SHO, who is often a general practitioner trainee wishing to gain predominantly antenatal and post-natal experience, is only exacerbating the problem of inappropriate analgesia in labour and as chairman of the Hospital Recognition Committee perhaps he should have been denouncing this practice as out-dated and dangerous. The institution of epidural analgesia should be left solely with the anaesthetist and the topping-up of epidurals should be shared between the midwife and the anaesthetist.

The work of the junior obstetrician is already recognized as intensive (Dowie 1989) and this small change will not only ease the workload, but it will also improve patient safety.

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Role of prostaglandin in the management of prelabour rupture of the membranes at term

Dear Sir,

In the study by Mahmood *et al.* (1992) on the use of vaginal prostaglandins in the treatment of prelabour rupture of membranes at term, they had two patients who were delivered by caesarean section for fetal distress. Both patients were in the group treated with vaginal prostaglandins and it is stated that uterine hyperstimulation occurred. They suggest that this may be caused by uncontrolled prostaglandin absorption into the amniotic cavity or the maternal circulation.

We have measured the level of prostaglandins in the maternal circulation in such circumstances. We found that the levels of prostaglandin E metabolite prior to treatment was approximately 10 times higher than that which is normally achieved after vaginal PGE$_2$ treatment when the membranes are intact. The level of prostaglandin E metabolite within the maternal circulation did not significantly increase after treatment (Fig. 1) The high level of prostaglandin E metabolite presumably reflects endogenous production of PGE$_2$ following rupture of the membranes and any exogenous PGE$_2$ which enters the circulation following treatment is insignificant in comparison.

Any effect which vaginal PGE$_2$ may have in the presence of ruptured membranes must therefore be at a local level either directly into the amniotic fluid or into the uterus. Alternatively, in view of the high levels of prostaglandin E metabolite in the circulation, the hyperstimulation seen in Mahmood's study may represent an idiosyncratic rather than a dose-related pehnomenon.

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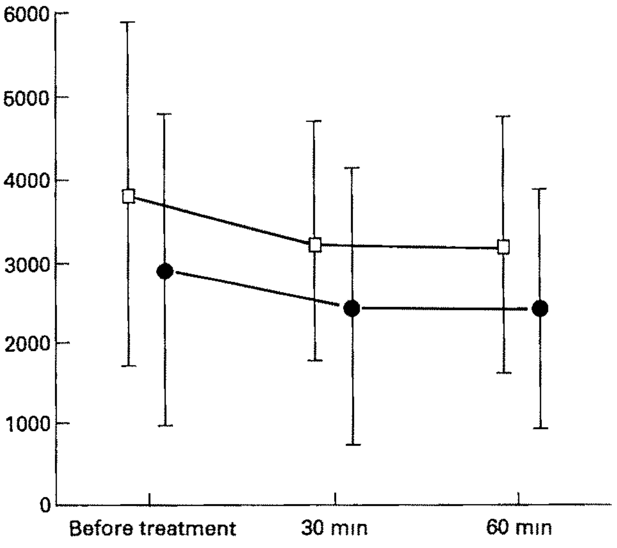

Fig. 1. Maternal serum levels of prostaglandin E metabolite following application of vaginal PGE$_2$ gel. □ = Unfavourable cervix 2 m PGE$_2$, ● = Favourable cervix 1 mg PGE$_2$

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Colposcopically directed punch biopsy: a potentially misleading investigation

Dear Sir,

Beeby (Correspondence 1992) correctly points out that the discrepancy between the histological diagnosis of CIN achieved by loop and punch biopsy reported by Buxton *et al.* (1991) may be over-estimated due to the design of their study. However, if further available evidence is considered, it is wrong to conclude that the limitation of punch biopsy was overstated. Allowance was made for all his criticisms in an earlier study (Howe & Vincenti 1991): punch biopsies were taken immediately prior to the loop specimen, during the same consultation; all specimens were examined by the same pathologist to prevent inter-observer variation confounding the results· the difference between specimens was only considered significant if punch biopsy failed to detect CIN found on the loop specimen or if micro-invasion or adenocarcinoma-in-situ were overlooked. Using these criteria punch biopsy resulted in a significant under-diagnosis in 24% of women. Furthermore, two similar studies comparing the histological diagnosis from punch biopsy with that from local excision by laser cone (McIndoe *et al.* 1989, Skehan *et al* 1990), reported similar findings, although both were subject to the same methodological errors as Buxton's study. Buxton *et al.* (1991) correctly conclude that these findings must cast doubt on any studies which use punch biopsy as their diagnostic method for CIN.

Are the discrepancies important clinically? Microinvasive disease was missed by punch biopsy in 1–2% of women in all four of the above studies. Furthermore, following the introduction of local ablation as treatment for CIN, McIndoe *et al.* (1989) noted a fall in the proportion of women found to have microinvasion suggested that it was being inadvertently ablated The inaccuracy of punch biopsy will, at the very least lead to delay in the treatment of minor grades of dysplasia, and deaths have occurred as a result of failure to recognize occult invasion (Ali *et al* 1986). Local excision offers two further benefits, by increasing the detection rate of adenocarcinoma-in-situ, and by providing information about whether a lesion is fully excised.

The reduced morbidity of the new excisional techniques when compared with knife cone biopsy, and inceasing mistrust of the accuracy of punch biopsy, is encouraging many clinicians to move away from local ablative treatment for CIN.

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BOOK REVIEWS

Vaginitis and Vaginosis edited by Benson J Horowitz & Per-Anders Mardh. Wiley-Liss, New York, Chichester 1991, 274 pages, with figures and tables, $59.95.

The contributors to this book read as a 'who's who' in vaginal pathophysiology and include many of the most active research workers in this area; Mardh, Eschenbach, Thomason, Sobel, Faro, Ison, Hillier, Holst, etc. Twenty seven of the 32 contributors are North American and as such the book has a chiefly American approach to patient management.

The book is divided into seven chapters: the vaginal ecosystem, epidemiology, office and laboratory diagnosis, implications of vaginitis, noninfectious vaginal conditions, therapy and recurrence and relapse Each chapter comprises three to nine papers by the various contributors and these are of variable length and quality, reflecting the particular expertise of the author In some areas, e.g , diagnosis of bacterial vaginosis, there is considerable but probably unavoidable repetition of information whilst in others there appear to be some notable omissions. The index contains a reference to *Weeksella virosa* (which was a new bacterium to me) but has no mention of *Staphylococcus aureus* of toxic tampon fame or of Group A beta haemolytic streptococcal infection, which rarely affects the vagina but is potentially life threatening and is therefore at present of clinical importance to doctors involved in the management of genital tract infections. These minor criticisms aside I would strongly recommend the book to genito-urinary physicians, gynaecologists and dermatologists since it covers many of the grey areas where these specialties overlap and occasional help is needed. It is not a book for beginners or for those expecting a fully comprehensive review of vaginitis/vaginosis but it is a book for those who need to keep up with the latest developments in vulvo-vaginal pathphysiology and for those who need a good source of references for research work. It will not be left on the shelf for long and will prove a useful source of information for those problem cases where all conventional therapy has failed.

A. L. Blackwell

Maternal Mortality. A Global Factbook edited by Carla AbouZahr & Erica Royston. World Health Organization, Geneva, 1991, 598 pages, with figures and tables, Sw fr50.

'Every minute of every day a woman dies as a result of pregnancy or childbirth somewhere in the world' So begins Angele Petros-Barvazian, the Director of the Division of Family Health, WHO, in the forward to this book Like many of the statistics revealed in the book it may come as quite a shock. In the 'developed' world we have long ago stopped using maternal mortality as an index of the quality of health care because the event is such a rarity; not so in the developing world

This book is not light reading. The great bulk of the text is given over to tables and descriptive text of the available information concerning maternal mortality in every developing country with a population of over 200 000. Exceptions to this rule are made for smaller countries where there would appear to be particularly interesting information For each country a chapter has been compiled in a standard form. The chapters are divided into the following sections:

1 Basic indicators (demographic, social and economic); 2 Health services (health expenditure, primary health care, coverage of maternity care), 3. Community studies, 4 Hospital studies; 5. Civil registration data/government estimates; 6. Other sources/estimates; 7 Selected annotated bibliography, 8. Further reading, 9 Data sources.

The first chapter is a short introduction The second is entitled 'The Global Picture' and really is mandatory reading for anyone with an interest in obstetric care and maternal mortality worldwide. The information contained in it is too great and too diverse to describe even briefly in this review but for example it estimates that for women in some of the poorer parts of Africa and Asia the chance of a woman dying is approximately one in 140 each time she becomes pregnant! Furthermore, because of relatively high parity in many poor countries, she will run this risk more often, so that in some parts of Africa the lifetime risk of dying from pregnancy-related causes may be as high as one in 15. A surprising revelation is the disparity in maternal mortality in the continent of Asia with rates of 4, 7, and 11 per 100 000 in Hong Kong, Singapore and Japan contrasting starkly with 1000 and 718 per 100 000 in the Yemen and Bali, respectively.

The third chapter is entitled 'Measuring Maternal Mortality' and attempts to qualify and verify the data presented in this book. The authors make no attempt to exaggerate the data presented, there is no need It is more likely that their data under-represent the awful state of health of most women entering pregnancy worldwide But the data is incomplete Cause of death is only reported in 78 countries, their combined populations representing just 35% of the world's total.

The fourth chapter details carefully how to read a country's profile in the following chapters. Finally, there is a single table of maternal mortality data for the developed world.

This tome has been carefully prepared and is thoroughly referenced, mostly by WHO publications. It 'has been compiled in order to share with everyone working for safe motherhood the rich and highly instructive collection of materials which WHO has assembled in the course of its work'. It is aimed primarily at decision makers who influence maternal care. In this task AbouZahr and Royston are to be congratulated. It is likely that this factbook will be the reference work for many years. In conclusion, the book offers no programme for combating the problem of maternal mortality. Interested readers are referred to the companion volume: 'Preventing Maternal Deaths' by Erica Royston and Sue Armstrong (WHO 1989).

Walter Prendiville

Maternal Mortality—The Way Forward. Some implications of the Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985–1987 by Naren Patel.

This book is based on the Proceedings of a Post Graduate Meeting held at the RCOG in January 1992, 96 pages, with figures and tables. Available from The Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG, £7.00.

The extension of Confidential Enquiries into Maternal Deaths in England and Wales to the United Kingdom was commemorated by a Postgraduate Meeting at the Royal College of Obstetricians and Gynaecologists in January 1992, and the proceedings published as 'Maternal Mortality—The Way Forward'

The widespread endothelial damage inflicted by pre-eclampsia is described and there are protocols for in-patient and daycare management. The British Eclampsia Survey of the United Kingdom throughout 1992 is outlined

Patients at heightened risk of massive haemorrhage are identified and there are detailed protocols for obstetricians and anaesthetists when it occurs. Also a precise list of the contents of a major haemorrhage trolley. A haematologist gives a clear description of disseminated intravascular coagulation and how to maximize laboratory assistance Aids to the early recognition of ectopic pregnancy are stressed.

Pulmonary embolism, the largest cause of death in the recently published 1985–1987 United Kingdom Report, is comprehensively covered and there are flow charts to apply when deep vein thrombosis, minor or massive embolism, is suspected.

The only shortcoming is the omission of indirect deaths, which contributed 38% of direct and indirect deaths, and despite cardiac disease ranking third overall.

This book will appeal to candidates for the membership examination and although it extensively complements the Report some reference to the full text will be necessary It is a worthwhile purchase for departmental libraries.

H. H. Francis

The Extracellular Matrix of the Uterus, Cervix and Fetal Membranes: Synthesis, Degradation and Hormonal Regulation edited by Phyllis C. Leppert & J. Frederick Woessner. Perinatal Press, Ithaca, New York, 1991, 284 pages, with figures and tables, US$110.00 (prepaid discount price $88.00).

This book compiles the proceedings from the symposium on Extracellular Matrix and the Reproductive Tract held in Rochester, New York, in May 1990. It is well-printed with good quality figures, tables and illustrations, not the cheaply produced edition that often follows these symposia

It is divided into four parts: overview of the matrix, the cervix, the uterus and fetal membranes and other tissues; it contains 31 chapters which are too many for a book of this size, and in fact some chapters are little more than abstracts. I attended a similar symposium in Oxford in 1980 and thought then that connective tissue biochemistry was a very difficult subject, it isn't any easier a decade later. The number of known collagen types and proteoglycans has nearly quadrupled, several new collagenases and other matrix metalloproteinases have been identified and a series of glycoproteins have been shown to be involved in physiological changes in the matrix and cell-matrix interactions.

The book offers some help in describing the progress over the past decade, but I wish more space had been given to the opening general chapters so that recent advances in protein structure and gene expression could be assimilated by the reader before moving to more specific experiments and measurements in a variety of human and animal tissues. Because of the large number of chapters and the brevity of some contributions it is difficult to give an overall picture of the book. Often what seemed promised by a grand chapter title was not delivered be the contents and the conclusions The clinician will feel frustrated when looking for explanations for premature rupture of the membranes or for recommendations to ripen the cervix; there is still very little known about the mechanisms underlying these processes. The chapter on cervical ultrasound evaluation should cause concern to clinicians because of the poor correlation between estimation of cervical length by palpation and by vaginal ultrasound.

The publication clearly highlights the many areas where research needs to be done. It (together with its predecessors edited by Naftolin & Stubblefield (1980) and by Ellwood & Anderson (1981)) would be a useful overview for doctors and scientists specialising in this field, but I feel the clinical obstetrician and gynaecologist is better served by one of the available general textbooks.

A. Lopez Bernal

Books received some of which may be reviewed at a later date:

Advanced Psychosomatic Research in Obstetrics and Gynecology edited by D. Richter, J. Bitzer & P. Nijs Springer-Verlag, Berlin, 262 pages with figures and tables, DM 128.00.

An Atlas of Ultrasonography in Obstetrics & Gynecology edited by Asim Kurjak. Parthenon Publishing, Lancs, 1992, 229 pages, £85.00.

Doppler Ultrasound in Perinatal Medicine edited by J. Malcolm Pearce. Oxford Medical Press, Oxford, 1992, 346 pages, £50.00.

Effective Care of the Newborn Infant edited by John C. Sinclaire & Michael B. Bracken. Oxford University Press, Oxford, 1992, 650 pages, £95 00.

Fetal and Infant Origins of Adult Disease edited by D. J. P. Barker. British Medical Journal, London, 1992, 335 pages, £24.95

Gynaecology edited by V. R. Tindall. Gower Medical, London, 1992, 191 pages.

Oxford Reviews of Reproductive Biology edited by S. R. Milligan. Oxford University Press, Oxford, 1992, 374 pages.

Practical Manual of Operative Laparoscopy and Hysteroscopy edited by Ricardo Azziz & Ana Alvarez Murphy Springer-Verlag, Berlin, 1992, 228 pages with figures, DM 128.00

Pregnancy Care in the 1990s edited by Geoffrey Chamberlain & Luke Zander. Parthenon Publishing, Lancs, 1992, 197 pages.

Surgical Obstetrics edited by Warren C Plauche, John C. Morrison & Mary Jo O'Sullivan. W B. Saunders, London, 1992, 512 pages, fully illustrated, £52.00

Twins and Higher Multiple Births edited by Elizabeth Bryan. Edward Arnold, London, 1992

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Further details can be obtained from:
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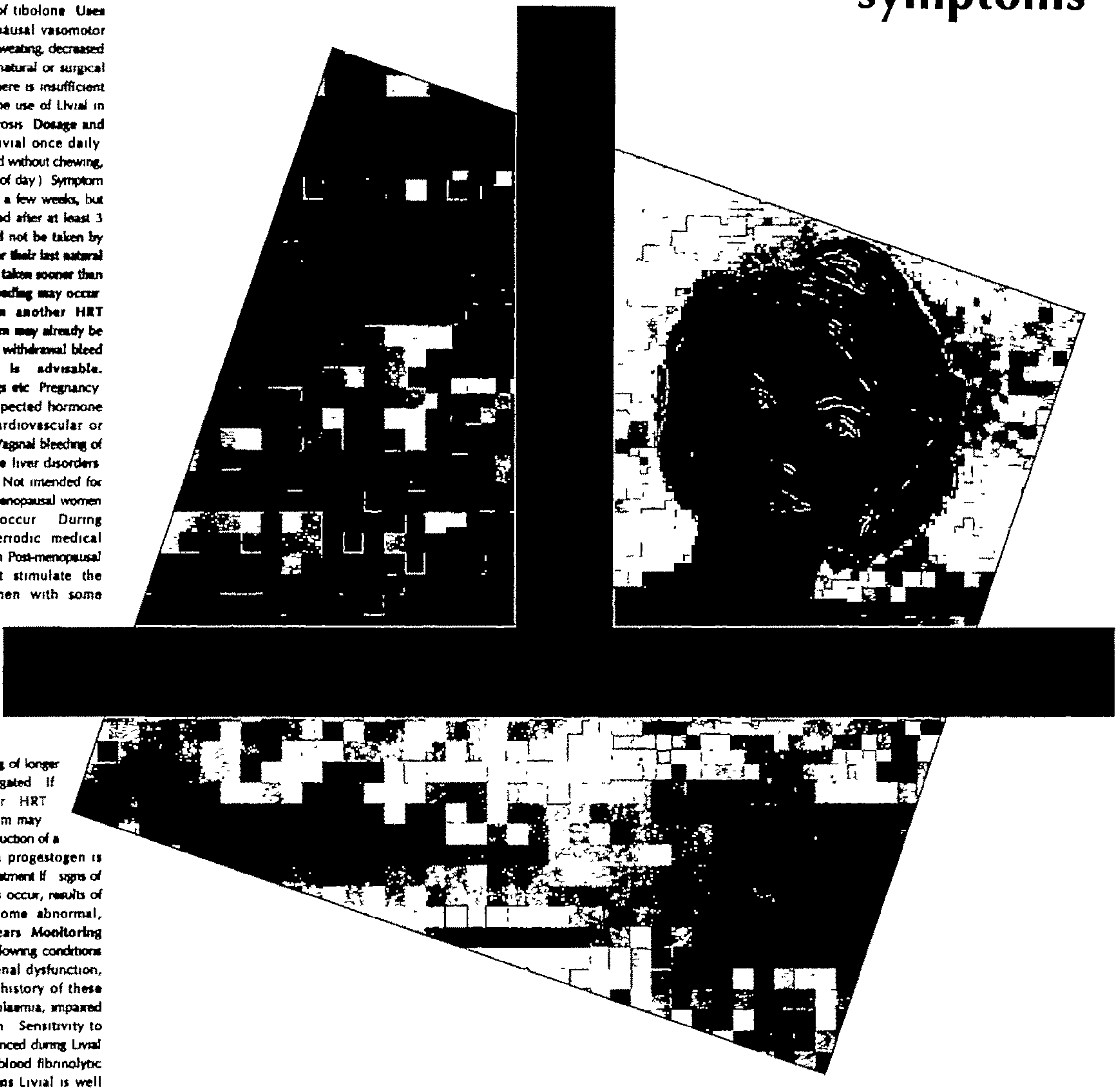

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6 reasons why more doctors prescribe Prempak-C and Premarin than any other HRT.

50 YEARS EXPERIENCE

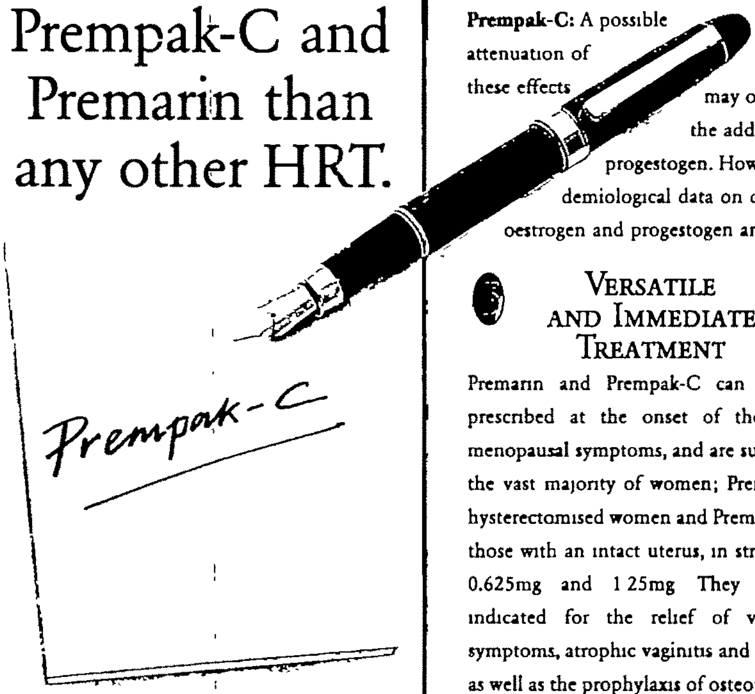
Premarin, a natural conjugated oestrogen, which is also used in the formulation of Prempak-C, is the only oestrogen used in any HRT with 50 years experience. The majority of long term studies, therefore, relate to the conjugated oestrogen found only in these products

LONG TERM SAFETY - BREAST CANCER?

Both doctors and patients are justifiably concerned about the potential risks of breast cancer for women taking HRT. Whilst there is suggestive evidence of a small increased risk of breast cancer with long-term HRT (greater than 5 years), this varies with the type and dose of the oestrogen used However, a recent comprehensive review of 31 studies provides evidence that menopausal therapy consisting of 0 625mg/day of conjugated oestrogens does not increase the risk of breast cancer.[1] Most studies, in fact, relate to conjugated oestrogen and so there is insufficient data to arrive at similar conclusions for any other regimen.

PROPHYLAXIS OF OSTEOPOROSIS

Prempak-C and Premarin are both indicated for the prophylaxis of osteoporosis in women at risk of developing fractures. A minimum daily dose of 0.625mg Premarin preserves bone mass, therefore reducing the risk of debilitating injuries such as hip fractures, by up to 66%[2,3] Further estimates suggest that prescribing Premarin for at least 10 years will reduce the risk of mortality linked to osteoporosis by 60%.[4]



REDUCING CARDIOVASCULAR DISEASE RISKS

Premarin: A recent review of considerable epidemiological evidence has shown, overall, a 50% reduction in risk of coronary disease in oestrogen users The most common form of oestrogen used in all these studies was conjugated oestrogen, i.e. Premarin

Prempak-C: A possible attenuation of these effects may occur with the addition of a progestogen. However, epidemiological data on combined oestrogen and progestogen are limited

VERSATILE AND IMMEDIATE TREATMENT

Premarin and Prempak-C can both be prescribed at the onset of the earliest menopausal symptoms, and are suitable for the vast majority of women; Premarin for hysterectomised women and Prempak-C for those with an intact uterus, in strengths of 0.625mg and 1 25mg They are also indicated for the relief of vasomotor symptoms, atrophic vaginitis and urethritis, as well as the prophylaxis of osteoporosis in women at risk

COST EFFECTIVE

Treatment costs are becoming increasingly important, especially as long term therapy can last from 5 to 10 years or longer. Compared to other forms of HRT, Wyeth's products cost remarkably little; Premarin costs just £1.84 and Prempak-C costs £4.06, for 28 days of therapy[7]

PREMPAK-C
PREMARIN

ABBREVIATED PRESCRIBING INFORMATION

PREMARIN* **USES**: Menopausal and post menopausal oestrogen therapy in women without a uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures

DOSAGE AND ADMINISTRATION: Natural conjugated oestrogens 0 625mg - 1 25mg daily Continuous administration is recommended In women with an intact uterus the addition of a progestogen for 10-12 days per cycle is essential

CONTRA-INDICATIONS: Known or suspected pregnancy and during lactation History of known or suspected cancer of the breast Oestrogen dependent neoplasia Undiagnosed abnormal genital bleeding Active thrombophlebitis or thromboembolic disorders Acute or chronic liver disease Rotor or Dubin-Johnson syndrome Severe cardiac or renal disease

WARNINGS AND PRECAUTIONS: Some studies have reported a small increased risk of breast cancer in long term oestrogen replacement therapy users (greater than 5 years), others however have not shown this relationship It is not known whether concurrent progestogen influences this risk The risk of endometrial hyperplasia and carcinoma with unopposed oestrogen use is lowered by the addition of a progestogen Diseases that may deteriorate during therapy include otosclerosis, multiple sclerosis, systemic lupus erythematosis, porphyria, melanoma, epilepsy, migraine and asthma Use with caution in patients with pre-existing uterine fibroids, endometriosis, breast nodules, fibrocystic disease, and in those with a history of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, cardiac or renal dysfunction Discontinue if jaundice, migraine, visual disturbances, thromboembolic phenomena or significant hypertension develop Certain endocrine and liver function tests may be affected Rarely idiosyncratic hypertension may occur Discontinue treatment prior to surgery or prolonged immobilisation Gallbladder disease Insulin requirements may be altered Premarin is not an oral contraceptive

SIDE EFFECTS: The following have been reported with oestrogen therapy premenstrual-like syndrome, increase in size of uterine fibromyomata, vaginal candidiasis, changes in cervical erosion and secretion, cystitis-like syndrome, breast changes, gastrointestinal symptoms, chloasma, melasma, erythema multiforme, erythema nodosum, haemorrhagic eruption, alopecia, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headaches, migraine, dizziness, mental depression, chorea, weight changes, reduced carbohydrate tolerance, aggravation of porphyria, oedema, changes in libido, leg cramps

PRODUCT LICENCE NUMBERS: Premarin 0 625mg PL0011/0165 Premarin 1 25mg PL0011/0166 Premarin 2 5mg PL0011/0167 **BASIC NHS PRICE** Premarin 0 625mg £1 84 (28 days) For full prescribing information please refer to data sheet

PREMPAK-C **USES** Menopausal and postmenopausal oestrogen therapy for women with an intact uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures.

DOSAGE AND ADMINISTRATION: Natural conjugated oestrogens 0 625mg - 1 25mg daily and one norgestrel 0 15mg tablet should be taken daily from day 17 to day 28 of oestrogen therapy

CONTRA-INDICATIONS: As for Premarin

WARNINGS AND PRECAUTIONS. As for Premarin Prempak-C is not an oral contraceptive

SIDE EFFECTS. As for Premarin Breakthrough bleeding and spotting Change in menstrual flow, dysmenorrhoea, amenorrhoea

PRODUCT LICENCE NUMBERS Prempak-C 0 625mg PL0011/0161 Prempak-C 1 25mg PL0011/0162

BASIC NHS PRICE: £4 06 - 28 days For full prescribing information please refer to data sheet

REFERENCES 1 Dupont W D and Page D L (1991) Arch Int Med 151, 67-72 2 Lindsay R et al (1984) Obstet Gynecol 63, 759-763 3 Kiel D P et al (1987) NEJM, 317, 1169-1174 4 Ross R K et al (1989) Lancet, 1, 505 5 Stampfer M.J and Colditz G A (1991) Prev Med, 20, 47-63 6 Stampfer M J et al (1991) NEJM, 325, 756-762 7 MIMs June 1992

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PREMARIN*
(Conjugated Oestrogens)

Wyeth Laboratories, Huntercombe Lane South,
Taplow, Maidenhead, Berkshire SL6 0PH.

PREMPAK-C*
(Conjugated Oestrogens + Norgestrel)

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COMMENTARIES

Contact lenses in pregnancy

The marked systemic changes of normal pregnancy (Chamberlain 1991) vary so widely that it is difficult to outline the typical ocular characteristics of a normal pregnancy (Sunness 1988). This is further compounded by the fact that a particular tissue response to two successive pregnancies in the same individual can be very different. Ocular anterior segment disturbances associated with conception may be mild, moderate or severe, with varying effects on a contact lens wearer (Imafidon 1991). As three quarters of the female population of contact lens wearers are of child-bearing potential (Asota & Imafidon 1992), there is a new impetus to investigate ocular signs and symptoms during pregnancy.

A recent report of ocular symptomatology of lens wear in multi-gravid patients recorded that 30% of established soft and rigid contact lens wearers experienced some difficulties during normal pregnancy (Imafidon *et al.* 1991). They used different commercially available care products Discomfort was the commonest complaint, and this was more associated with the wearing of rigid lenses. Other symptoms were persistent greasing of the contact lens (that is, surface mucous deposition), increased lens awareness, and reduced wearing time. Although the severity of a condition as revealed by symptoms does not always correlate with clinical signs, these complaints suggest an inadequate anterior ocular surface lubrication and that the tears may have undergone some changes in quality and/or quantity.

Changes in tear production

Using the most frequently performed clinical tear test, the Schirmer (1903) test, Imafidon *et al.* (1992) observed a marked decrease in tear production, particularly during the third trimester of gestation, in approximately 80% of a study population. Although modifications to the Schirmer test as suggested by Mackie and Seal (1981) were used in this study, the test has been found to be very specific (90%) but not particularly sensitive (25%) (Lucca *et al.* 1990). Despite the limitations of this assessment technique, there is probably a relative decrease in tear volume during pregnancy. Any foreign body disturbs the tear film and the additional stress placed on the lacrimal system by the insertion of a contact lens will reduce the tolerance threshold which in some cases results in outright intolerance or a temporary discontinuation of wear (Mackie 1985).

It has been suggested that the altered composition of the trilaminar tear film is in favour of the inner mucus layer (Milder 1987). This could be due to a reduced production of aqueous or an increased secretion of mucin. The on-going study on tear quality should provide a better insight (Imafidon *et al* 1992). Mucin is produced by the goblet cells of the conjunctival surface. A decrease in goblet cell population results in reduced secretion and this has been observed in association with raised level of steroidal hormones such as oestrogens and progestogens (Imafidon 1991).

Corneal changes

The cornea contains about 70% water and is the single anterior segment dimension most affected by pregnancy due to changes in extracellular fluid. High plasma concentration of some steroidal pregnancy-related hormones causes electrolyte imbalance leading to tissue hydration and oedema The hypoxic effects of some contact lenses carry with them a risk of further stress. Pachyometric studies confirm that central corneal thickness increases during uncomplicated pregnancy by levels as high as 16 microns (Weinreb *et al.* 1988).

The sensitivity of the cornea is reduced in pregnancy, thus compromising the corneal defence mechanism. Recent studies show that in about 85% of cases, there is a measurable amount of corneal hypoaesthesia (Millidot 1977) making patients totally unaware of irritations or abrasions until more serious sequelae develop.

Corneal curvature readings have shown some increase in dioptric values during pregnancy (Park *et al.* 1992) The keratometric assessment in each trimester showed a statistically significant difference between the first and the third trimesters. This confirms earlier reports which show a clear trend of corneal steepening with changes of 0·25 to 1·50 diopters. Imafidon (1991) attributed this disparity to the extensive individual variation which is characteristic of pregnancy. A similar steepening has also been noted with raised levels of oestrogens in patients on oral contraceptives (Farrall 1974) The clinical significance of the changed corneal shape is that previously well-fitted lenses may exhibit a less than optimum lens/cornea relationship. This may make other changes more pronounced or nullify their clinical effects, depending on pre-existing conditions.

General ocular alteration

Other difficulties accompanying lens wear in pregnancy have been linked to conjunctival modifications such as an increased epithelial cell maturation index, arteriolar spasm in conjunctival vessels, constriction of the arterioles and reduced blood flow. Lid oedema may lead to extreme discomfort if the margins are inflamed (Imafidon 1990).

In pregnancy, the water permeability of the crystalline lens within the eye increases, and the curvature of this lens also steepens. The refractive status of the eye can experience a myopia shift up to about 1·25 diopters. The visual correction which was based on pre-gestation findings becomes inadequate. Visual field contraction, attributed to pituitary gland enlargement, and gestational ocular hypotension have been reported (Sunness 1988).

Contact lens materials

Surface deposition on a contact lens produces discomfort; the degree of deposition is related to the material from which it is made. The first generation rigid gas permeable lenses which were made of cellulose acetate butyrate (CAB) which had greater affinity for lipid deposits compared to polymethyl methacrylate (PMMA) or newer generation fluorinated silicone acrylates (Atkinson 1988). Soft lenses of high ionicity (that is, higher negative surface change) manifest a greater affinity for deposits, particularly proteins, than non-ionic lenses (Imafidon 1988). The rate of deposit build-up due to altered composition of tears will very much depend on the lens material. Alcohol-based lens surfactant cleaners have been helpful in removing deposits but the rate of accumulation after cleaning can be quite high.

Conclusion

The quantity and quality of human tears change during pregnancy. The presence of a foreign body such as a contact lens exacerbates any subtle sub-clinical changes. A greater manifestation is seen in established contact lens patients who had asymptomatic pre-gestation marginally reduced lacrimal liquid out-put, or those who were not fully adapted to their lenses before pregnancy. There have been patients who successfully wore their lenses throughout pregnancy and only started having difficulties some weeks postpartum. The whole question of symptomatology in pregnancy can be better answered when the trend, degree and extent of all the modifications secondary to normal pregnancy have been established.

Gestational conditions such as diabetes and hypertension will compound the changes already outlined. They all play a part in ocular symptomatology in pregnancy and this makes more studies desirable. There is therefore, a need for better controlled, and better designed studies which will utilize advanced techniques such as ultrasonic pachycometry, computerised carbon dioxide laser aesthesiometry, automated keratometry or videokeratoscopy, and less invasive assessment of tear volume.

If moderate to severe symptoms develop in extended wear patients, they should be first advised to reduce their wearing time and switch to daily wear only. The importance of regular examinations during this period cannot be over-emphasized. Positive slit lamp biomicroscopy findings and severe symptoms require immediate discontinuation. This will pre-empt any serious anterior segment pathologies.

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Antenatal HIV testing

The increase in heterosexually acquired HIV infection has led to a rise in the number of seropositive pregnant women and children at risk of perinatal HIV infection (Johnson & Webster 1990; Norman *et al.* 1990). Neonatal serosurveys claim that HIV prevalence in inner London rose from 1 in 2000 in 1988 to 1 in 500 in the first three months of 1991 (Adies *et al.* 1991). Offering HIV testing to antenatal women provides an unique opportunity of targeting the young sexually active population and making them aware of HIV infection while they are responsive to health education in their concern for the welfare of their unborn child. Anonymous unlinked antenatal HIV testing has been adopted in the USA and many European countries to provide some estimation of the seroprevalence in the heterosexual community. This method of testing is invaluable in providing epidemiological data but it is not useful to the individual woman, her unborn child or to those providing antenatal care as infected women cannot be identified.

The most widely adopted method of antenatal testing in the western world is to concentrate on high risk women and test those who consent. However, there are great limitations as many women do not know that they are at risk and a short interview at antenatal booking may fail to reveal high risk activities. High risk testing has been shown in several studies to miss a significant proportion of women who are seropositive. Obstetricians were aware of only 20% of maternal HIV infections identified by anonymous neonatal screening in three Thames regions between 1988 and 1991 (Adies *et al.* 1991). In an inner city area of Baltimore, HIV detection was raised to 87% from 57% when offered to all antenatal women and not to just those who were identified as high risk (Barbacci 1991). The uptake of the test increased in both the non-high risk and high risk groups in this study by offering HIV testing as a routine, so removing the stigma attached to singling out a specific group. In Scotland, where HIV testing is more accepted than in England, 80% of infected pregnancies identified by anonymous neonatal screening were already known to be so to their obstetricians (Tappin *et al.* 1991).

One of the arguments for implementing widespread antenatal HIV screening is that intrauterine infection does occur and accounts for the majority of HIV infection in children globally. The vertical transmission of HIV infection has been estimated to be approximately 13% by the recently reported European collaborative study group (European Collaborative Study 1991), while others have reported higher transmission rates (Italian Multicentre Study 1988; Hira *et al.* 1989; Ryder *et al.* 1989). Differences in reporting infected pregnancies and less rigorous or prolonged follow-up of children born to seropositive mothers may in part explain these higher transmission rates reported, and vertical transmission rates reported in studies from Africa may not be a true representation of events in the developed world.

There is no method by which intrauterine infection can be determined, but there are certain factors which may influence maternal–fetal transmission. Women with advanced HIV infection are more likely to infect their offspring (Hira *et al.* 1989; Ryder *et al.* 1989), and breastfeeding plays a small but significant role in perinatal transmission.

The pregnancy outcome, for both mother and baby, is not significantly different between HIV positive and matched HIV negative women (Selwyn 1989; Minkoff *et al.* 1990a; European Collaborative Study 1991), although some groups have reported that babies born to seropositive women were more likely to be premature and of lower birth weight (Hira *et al.* 1989; Braddick *et al.* 1990).

The obstetric management of the HIV seropositive woman is little different to that of her seronegative counterpart but knowledge of her status allows close monitoring of the HIV infection and drug treatment to be instituted promptly if complications occur. It appears that pregnancy does not affect the course of HIV infection in the asymptomatic individual, but women with advanced HIV infection are at risk of severe opportunistic infections whilst pregnant (Minkoff *et al.* 1990b). These women benefit from antiretroviral therapy. Recent reports of the use of Zidovudine in pregnancy are reassuring as there have been no fetal malformations, excess prematurity, or fetal toxicity attributed to the use of this drug in HIV infected women (Sperling *et al.* 1992). Knowing the status of the pregnant woman also allows the infant born to a seropositive mother to be monitored postnatally and followed-up appropriately by the paediatrician for evidence of acquired infection.

With these advantages why is HIV screening controversial? The test cannot predict the transmission of HIV to the fetus. It can take 12 weeks for seroconversion to occur during which time the woman may be most infectious. A negative test at the beginning of pregnancy may not be indicative of HIV status at delivery and efforts must be made to emphasize methods of reducing new exposure to HIV infection. There is concern as there is no cure for HIV. Offering HIV testing may cause severe emotional distress but there is evidence that once a woman is found to have a negative test there is no further anxiety related to HIV status during the rest of the pregnancy (Larsson *et al.* 1990). It has been suggested that a negative test result gives permission for adopting risky behaviour. Worries regarding discrimination by life insurance companies on disclosure of an HIV test can now be allayed since their clear statement not to penalise those tested as part of an antenatal screening programme, providing the test is negative.

Finally, there is the objection that implementing voluntary HIV screening to all pregnant women would result in an enormous increase in workload in antenatal clinics, require specialist HIV counsellors, and would not be cost effective in terms of the prevalence of HIV infection.

The antenatal booking clinic provides the ideal opportunity to raise the issue of HIV testing at the same time as the other prenatal screening programmes which are routinely being performed. Counselling is not a new or difficult skill for midwives and doctors responsible for the care of pregnant women. This pre-test HIV counselling should normally be short and unambiguous with the possibility of specialist HIV/AIDS counsellors available for specific cases in much the same way as referrals to specialist genetic counsellors are necessary. The use of written leaflets about HIV infection and AIDS are helpful but do not substitute for pre-test counselling (Sherr & Hedge 1990). The time between the test and result should be short. This should not create extra visits as the HIV result can be given at the same time as the results of the other investigations performed at the booking visit. A positive test result can be given with support from the HIV/AIDS counselling services.

Any screening programme must be cost effective, acceptable to the public and ultimately reduce the disease prevalence. The cost of implementing routine antenatal testing must be weighed up against the prevalence of HIV infection both in the UK as a whole and in individual areas. With the seroprevalence of HIV infection outside London remaining stable at 1 in 16 000, there is no case for instituting HIV testing as a routine investigation. We would suggest that in these areas of low seroprevalence it should be discussed with women during their antenatal booking visit and only offered to those who have an identified risk factor. However, in areas with higher seroprevalence, such as inner London, we believe it should now be offered routinely. Pre-test counselling should be brief, given by a midwife who has undergone training and testing undertaken of those giving consent. By making HIV testing more routine and thus less stigmatising, more people will be aware of possible HIV infection and accept the case for routine screening.

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OBSTETRICS

The variability of urinary protein and creatinine excretion in patients with gestational proteinuric hypertension

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ABSTRACT

Objective To determine the variability of protein excretion in patients with proteinuric hypertension and the accuracy of either a urinary protein/creatinine ratio or a Multistix examination for the estimation of a 24 h protein excretion.

Design An indwelling urinary catheter was placed for 24 h and successive 8 h specimens examined.

Setting A tertiary referral hospital in Cape Town, South Africa.

Subjects 22 women with significant proteinuria in pregnancy were studied.

Main outcome measures The urine volume, protein excretion and creatinine excretion in eight hourly periods were measured. Multistix examination of each specimen was recorded.

Results A large coefficient of variation in urine volume (41%), amount of protein excreted (44%) and the amount of creatinine excreted (22%) in the eight hourly specimens were noted. The protein creatinine ratio did not accurately predict the 24 h protein excretion. The Multistix examination was less accurate with increasing amounts of proteinuria. The amount of creatinine excreted correlated with the volume of urine passed (r = 0·43).

Conclusion The analysis of a 24 h specimen or urine for protein excretion remains the best method of monitoring proteinuria in pregnancy. The amount of creatinine excreted in 24 h cannot be used as an index of completeness of collection of the 24 h specimen.

Abnormal or significant proteinuria in pregnancy is poorly defined. A small amount of albumin is normally excreted in the urine and this amount is probably not increased in pregnancy (Wright *et al.* 1987).

The upper limit of normal proteinuria in pregnancy is accepted at 300 mg/24 h (Davey and MacGillivray 1988). Once this level is exceeded for the first time after 20 weeks of gestation the diagnosis of gestational proteinuria, or if in association with hypertension, a diagnosis of gestational proteinuric hypertension can be made (Davey & MacGillivray 1988). Proteinuria is an important marker of the severity or progression of the disease process but the monitoring of the exact amount of protein excreted may be difficult in practice.

Once significant proteinuria is suspected the degree of proteinuria can be diagnosed and measured by: (1) 24 h urine collection; (2) spot testing of proteinuria at regular intervals; (3) a timed collection of urine and extrapolation to a 24 h value; or (4) urinary protein/creatinine ratio performed on a spot specimen.

Spot testing of proteinuria is used as a screening test at antenatal clinics and provides a measure of the concentration of protein in a given specimen. The protein concentration however is dependent on both the volume of urine and the amount of protein excreted in a given time. Chesley (1939) found that protein excretion varied up to five-fold in successive four hourly specimens and therefore spot testing may not indicate the true amount of protein excretion. In nonpregnant patients Shaw *et al.* (1983) found that the urine protein/creatinine ratio in spot specimens was very closely correlated with the protein excretion in a 24 h period. The collection of all urine passed for 24 h is not only inconvenient and difficult in outpatients, but 24 h urine collections are often incomplete unless patients are closely supervised. The use of protein/creatinine ratios in spot specimens in pregnant patients would overcome not only the problems of variation in urine and protein concentration but of the difficulties of 24 h urine collections.

This study was undertaken to investigate the variability of protein and creatinine excretion in successive timed specimens and to determine whether measurements of protein/creatinine ratio in single specimens of urine could provide a reliable guide to 24 h urine protein excretion in pregnancy.

Subjects and methods

Twenty-two pregnant women were studied after the diag-

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nosis of significant proteinuria (2+ or greater) had been made on routine spot testing of urine with a Multistix (Ames Division, Miles Laboratories Ltd, UK). Women were excluded if there was the possibility of delivery in 24 h or if they were confined to bed. To ensure a complete collection and avoid contamination by vaginal secretions an indwelling catheter was inserted for 24 h after previously emptying the bladder. Three urine collections were performed: from 14.00 h–22.00 h, 22.00 h–06.00 h and 06.00 h–14.00 h. Each of the three urine collections were analysed separately for the protein and creatinine concentration. At 08.00 h on the day of the study a serum creatinine and albumin was measured. On each of the urine specimens a Multistix test for protein was performed.

All urine specimens were collected without preservatives and refrigerated until analysis the next day. Analysis of the proteinuria was performed using the biuret method (Boehringer Mannheim Diagnostica 1987). The serum and urinary 'true' creatinine was measured as described by Sigma Diagnostics. The creatinine clearance (8 h creatinine clearance (ml/min) = urine volume (ml) × creatinine concentration (mmol/l)/serum creatinine (mmol/l) × 480) and protein/creatinine ratio (protein/creatinine ratio (mg/mmol) = urine protein concentration (mg/l)/urine creatinine concentration (mmol/l) were calculated. The women did not have their diet or activity restricted and the blood pressure was measured four hourly throughout the study period. Statistical analysis was performed using a one way analysis of variance and a coefficient of variation was also calculated from the three specimens. The study was approved by the Ethics and Research Committee of the University of Cape Town and all women gave written, informed consent to the study.

Table 1. Urinary variables studied from successive 8 h urine collections

	Means and standard deviation (SD)		
Variables	Specimen 1 14 h–22 h (n = 22)	Specimen 2 22 h–06 h (n = 22)	Specimen 3 06 h–14 h (n = 22)
Urine volume	832	720	706
(ml)	(412)	(562)	(336)
Protein concentration	2368	1963	2443
(mg/l)	(2653)	(2128)	(2008)
Protein amount	1315	940	1312
(mg/8 h)	(1085)	(714)	(1084)
Creatinine concentration	5·70	7·18	7·20
(mmol/l)	(3·51)	(5·90)	(5 58)
Creatinine amount	3·61	3·49	3·67
(mmol/8 h)	(0·98)	(1·34)	(1 07)
Protein/creatinine	490	448	474
ratio	(326)	(235)	(293)
Creatinine clearance	104	100	104
(ml/min)	(45)	(52)	(38)
Diastolic BP	92	90	93
(mmHg)	(12)	(10)	(12)
Mean arterial pressure	110	107	109
(mmHg)	(14)	(12)	(12)

Results

Urine creatinine, protein measurements (Table 1)

There was no significant changes in any of the results in the eight hourly timed collections. The protein excretion demonstrated a reduction during the period 22.00 h–06.00 h, but this fall was not significant. The protein concentration correlated with the creatinine concentration, the urine volume, the protein creatinine ratio and the amount of protein excreted per 8 h (Table 2). The protein/creatinine ratio correlated with the 24 h protein excretion (Specimen 1, r = 0·49, $P<0{\cdot}05$; Specimen 2, r = 0·36, $P>0{\cdot}05$; Specimen 3, r = 0·53, $P<0{\cdot}05$) (Fig. 1 demonstrates Specimen 3) and the urine volume did not correlate with the amount of protein excreted (Table 2). The Multistix estimation on a single spot specimen was found to be very variable with increasing amounts of proteinuria (Fig 2) and protein concentration (Fig. 3). The Multistix gave a false negative result in two specimens in which there was significant proteinuria. The coefficients of variation between measurements in the three successive specimens were wide, the largest being the protein concentration and the lowest the amount of creatinine excreted and the creatinine clearance (Table 3). It is notable that the total amount of creatinine correlated with the volume of urine suggesting that the excretion of creatinine in the urine in women with hypertensive disorders of pregnancy is not independent of the volume excreted (Table 2).

Discussion

One of the features of proteinuria in gestational proteinuric hypertension is that the variability in protein excretion in successive urine specimens appears to be greater than in renal disease outside of pregnancy. Chesley (1939) reported an up to five-fold variation of protein excreted in four hourly collections.

The assessment of changes in protein excretion is thus difficult and is open to clinical misinterpretation. The accepted

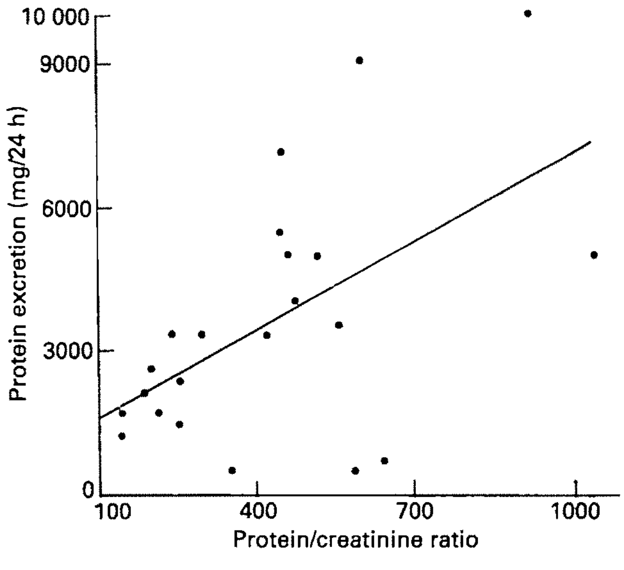

Fig. 1. The correlation of the protein creatinine ratio measured on Specimen 3 and the 24 h excretion of protein (r = 0·53).

Table 2. Correlation between urine volume, protein concentration and the other variables measured

	Correlation coefficients						
	Urine volume ml/8 h	Protein concentration mg/l	Protein amount mg/8 h	Creatinine concentration mmol/l	Creatinine amount mmol/8 h	Protein creatinine ratio	Creatinine clearance ml/min
Urine volume (ml/8 h)	—	–0·55	NS	–0·65	0·43	NS	0·40
Protein concentration (mg/l)	–0·55	—	0·57	0·63	NS	0·28	NS

NS = No significant correlation.

standard for the assessment of proteinuria is the measurement of the total protein excreted in a 24 h urine collection. The collection of urine over 24 h, however, is inconvenient, time consuming, and errors due to incomplete collections and spillage are common. It would be a great advantage if reliable measurements of protein excretion could be obtained from in single 'spot' specimens. The 'spot' protein/creatinine ratio has been shown to have a close correlation with the 24 h urinary protein excretion in nonpregnant patients (Shaw *et al.* 1983) and can be used to assess the protein excretion in nonpregnant women.

However, in the results presented the individual estimations of the protein/creatinine ratio in 8 h urine collections does not correlate to the same degree with the 24 h urine protein excretion (Specimen 1, r = 0·49, $P<0{\cdot}05$; Specimen 2, r = 0·36, $P>0{\cdot}05$; Specimen 3, r = 0·53, $P<0{\cdot}05$) when there is proteinuria in pregnancy. The large variation in the prediction of the 24 h protein excretion by the protein/creatinine ratio make this test unsuitable for clinical use. Specimen 3 demonstrated the best correlation and is shown in Fig. 1.

Although we could not demonstrate a significant reduction in proteinuria at night, it is not possible to extrapolate the protein measurements from the timed urine specimens to 24 h due to the large coefficient of variation (44%) (Table 3).

'Spot' testing of the urine does not provide a reliable indication of the changes in total protein excretion due to variation in the previous intake of fluids and dilution of the urine passed. Spot testing is useful for the screening of patients for proteinuria but not for the assessment of changes in amount of protein excreted. The only reliable measure of protein excretion is a 24 h urine collection preferably performed daily. Additional information can be obtained from a 24 h collection by simultaneously measuring the urine and serum creatinine, and the creatinine clearance can be used as a measure of changes in renal function.

The amount of creatinine excreted in successive 8 h col-

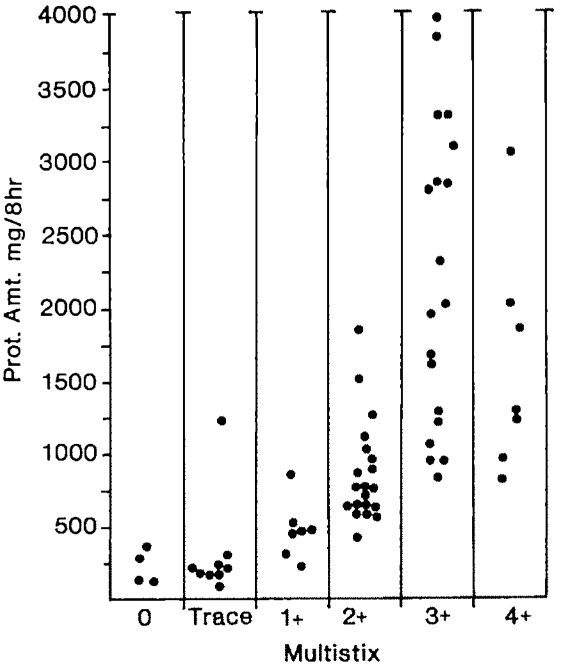

Fig. 2. The amount of proteinuria in 8 h specimens tested with a Multistix.

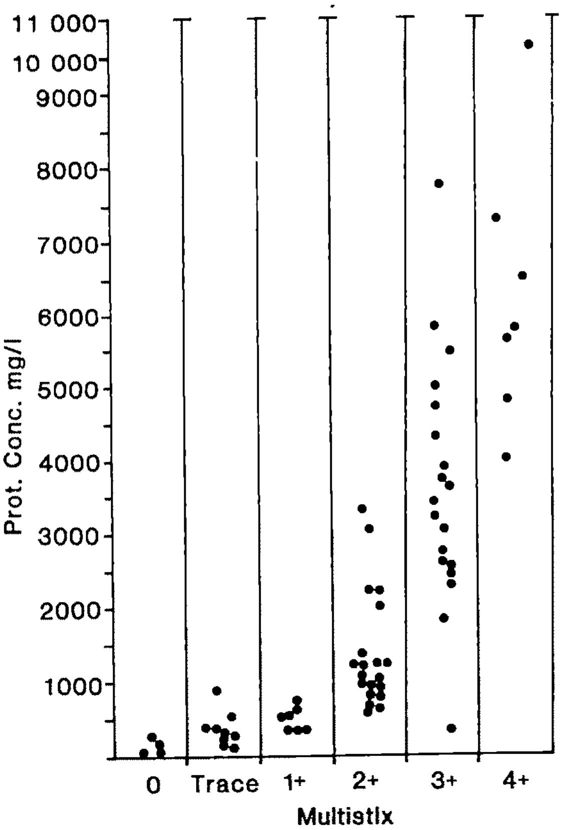

Fig. 3. The concentration of protein in 8 h specimens tested with a Multistix.

Table 3. Variability in urine protein and creatinine in three successive 8 h urine collections.

Coefficient of variations	%
Urine volume	41%
Protein concentration	50%
Protein amount	44%
Creatinine concentration	37%
Creatinine amount	22%
Protein/creatinine ratio	27%
Creatinine clearance	22%

lections shows considerable variation (Table 3) and tends to increase as the urine volume increases (Table 2). Measurement of total urine creatinine as an index of the completeness of the collection cannot be used in pregnant as in nonpregnant patients.

The increase in protein excretion in the waking hours is a feature of both pregnant and nonpregnant women. Exercise produces a 5–100 fold increase in urinary albumin (Poortmans & Jeanloz 1968). Urinary amylase and lyzosyme studies have shown that after exercise there is a marked decrease in the tubular reabsorption of filtered proteins (Poortmans 1972). It is thought that the marked increase in urinary proteins when standing upright and when exercising is due to a decrease in the reabsorption of filtered proteins in the proximal tubules secondary to decreased renal tubular blood flow. A similar mechanism in women with gestational hypertension may be responsible for the decrease in protein excretion whilst the woman is recumbent, but this reduction is not significant.

In conclusion, we have demonstrated that the excretion of protein in women with gestational proteinuric hypertension shows a considerable variation when measured in successive eight hourly urine collections. In addition we have shown that the urinary protein creatinine ratio cannot be used as a measure of 24 h urine protein excretion in pregnancy. It is therefore recommended that the measurement of total protein excretion in a 24 h urine collection should be used to confirm a diagnosisof proteinuria and for the measurement of changes in amount of protein excreted in women with proteinuria in pregnancy.

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OBSTETRICS

Prepregnancy counselling: experience from 1 075 cases

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ABSTRACT

Objective To assess the activity of a prepregnancy counselling clinic in terms of investigations, counselling, treatment and subsequent pregnancy outcome.
Design Review of 1 075 couples attending over a nine year period.
Setting University Hospital offering a tertiary referral service for fetal medicine.
Subjects Couples referred to the clinic from a variety of sources.
Main outcome measures Categories of referral, value of diagnostic tests, and subsequent pregnancy outcome.
Results The main categories of referral were: previous miscarriage (44·4%); previous fetal abnormality (19·6%); chronic maternal disease (22·3%); and others (13·7%). Routine investigations produced a low yield of abnoramality (1%), in contrast to investigations selected for specific reasons (12%). Subsequent pregnancy outcome, which was unaltered in either the previous miscarriage or fetal abnormality groups, did improve in the chronic maternal disease group.
Conclusions This study does not prove the value of prepregnancy counselling. However, it does illustrate the importance of making an accurate assessment of previous problems and current health as a means of determining both maternal and fetal risks in a subsequent pregnancy, a process which seems to lead to an improved outcome within selected groups. The importance of continuity of care in all couples, especially when there has been a previous adverse pregnancy outcome is emphasized.

The place of preconceptual care has undoubtedly become more established over the past decade as the complexity of counselling problems has increased (Smith *et al.* 1987). A brief discussion in a regular antenatal or gynecological clinic with a couple who have suffered a pregnancy loss is no longer appropriate or practical. The enhanced potential for prenatal diagnosis, the concepts surrounding fetal loss (Stirrat 1990) and the relationship between maternal disease and fetal outcome, for example in diabetes (Steel *et al.* 1982, 1990), all require comprehensive discussion. A prepregnancy clinic has existed in The Queen Mother's Hospital, Glasgow, since 1982. The purpose of this report is to describe an audit of its activity, with particular reference to subsequent pregnancy outcome.

Subjects and methods

Structure of the prepregnancy clinic

The clinic is held weekly and staffed by a consultant obstetrician, a full-time sister midwife, a fellow in fetal medicine, and other rotating junior staff. Couples are assessed initially by the sister midwife according to an agreed protocol: details of their history are collected and routine investigations are performed; other selected investigations may also be arranged at this stage, depending on the main problem (Table 1). Relevant information from other sources regarding previous pregnancies or medical disorders are also sought at this stage. Karyotype analysis is performed on the male partner if there is a history of miscarriage or previous fetal karyotype abnormality. No other male investigations are performed. The couple are reviewed by the medical staff approximately four weeks later, when decisions are taken regarding the necessity of any further investigations and the need for advice from other sources. The prospects for a future pregnancy are discussed with the couple and, if a further pregnancy is contemplated, a plan for care is offered.

Method of audit

The clinic records of all patients seen between 1982 and 1990, inclusive, were reviewed. Details of history, examination findings, results of investigations and subsequent follow up were collected prospectively into a computer database which was used to determine the major categories of referral, the value of investigations performed, and the prognostic indicators of subsequent pregnancy outcome.

Study definitions

A first trimester miscarriage was defined as loss of a pregnancy before 13 completed weeks gestation. Two spontaneous losses were termed repeated miscarriage, whereas three or more consecutive spontaneous losses were described as recurrent miscarriage.

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Table 1. Routine and selected investigations performed at the prepregnancy clinic.

Prepregnancy clinic investigations	
Routine investigations	Selected investigations
Full blood count	Serum iron
Urine culture	Serum ferritin
Plasma calcium & phosphate	Serum folate
Rubella serology	Blood group
Liver function tests	Viral serology:
	cytomegalovirus
	herpes simplex & zoster
	parvovirus
	Hepatitis B surface antigen
	Haemoglobin A1c
	Random blood sugar
	Glucose tolerance test
	Thyroid function tests
	Karyotype
	Cervical smear
	Cervical culture
	chlamydia trachomatis
	ureaplasma urealyticum
	trichomonas vaginalis
	mycoplasma hominis
	gardnerella vaginalis
	neisseria gonorrhoeae
	Hysterosalpinogography
	Cervical resistance studies
	Pelvic ultrasound
	Antinuclear factor
	Lupus anticoagulant

Statistical analysis

Continuous variables were described by mean and range. Differences in proportions were examined using the χ^2 test and interpreted by the 95% confidence interval (CI) for the differences between proportions with P values <0·05 considered significant (Gardner & Altman 1986).

Results

During the study period, 1 075 couples were seen. The majority (52%) were referred by consultant obstetricians, 22% were referred by other hospital specialists or general medical practitioners and 17% by family planning clinics. A small proportion (9%) were self-referred. The mean age of the women when first seen was 29 years (range 17–46) and the mean age of their partners was 31 years (range 18–62). A high proportion of couples (89%) were married, 5% were single, 1% were divorced and the remainder were in steady relationships. The social class profile (determined by the male partner's occupation) was professional (19%), managerial (17%), skilled manual (39%), unskilled manual (18%) and unemployed (7%). The majority (66%) of the women did not smoke but 7% admitted smoking more than 20 cigarettes per day. Seventy four per cent of the women were occasional alcohol consumers and 1% were considered to drink alcohol excessively. At the first visit 21% of the women were not using any contraception, 58% were using hormonal methods, 19% had intrauterine devices and 2% were using natural methods.

Eight hundred–thirty nine couples (78%) were discharged following a single consultation with the medical staff. This usually followed a previous fetal abnormality or anxiety about some aspect of pregnancy. The range of routine and selected investigations carried out at the prepregnancy clinic is shown in Table 1. A few (<1%) routine investigations were found to be abnormal, usually anaemia due to either a low serum ferritin or folate, which was treated appropriately. By contrast, 12% of all selected investigations were abnormal. These are described under the three major categories of referral.

Indications for referral

Three main categories were apparent: previous spontaneous miscarriage (478); previous fetal abnormality (211); and chronic maternal disease (240). A miscellaneous group (146) comprised mothers who had previously experienced a spontaneous preterm delivery, unexplained intrauterine death, severe pre-eclampsia or antepartum haemorrhage.

Outcome following previous miscarriage

Among this group, which comprised 478 couples, 275 had experienced one or more first trimester miscarriages, of whom 80 had a history of recurrent miscarriages. The remaining 203 couples had experienced miscarriages after 13 weeks gestation and 15 of them had suffered recurrent second trimester miscarriages. The results of the selected investigations in this group are shown in Table 2. Fifteen parental karyotypic abnormalities were detected (5·4% of the total number of couples screened). A balanced translocation was the most common abnormality, found in nine cases (3–13, 1–13 (3); 4–11, 4–7 (2); 12–16, 9–16) and the remaining six were pericentric inversions. Abnormal cervical resistance studies (Anthony *et al.* 1982) were found in half of the 14 women evaluated, all of whom had a cervical suture inserted at 14–16 weeks gestation in a subsequent pregnancy. Previously unsuspected or poorly controlled medical conditions were detected in 11 cases (hypothyroidism in two, diabetes mellitus in four, lupus inhibitor in five), which resulted in the institution of appropriate therapy either before or during a subsequent pregnancy. The highest proportion of abnormal investigations (40%) was found among couples with a history of recurrent second trimester miscarriages.

In this group, 238 couples (49%) had a further pregnancy. The proportion of live normal births was high (88%) and did not differ significantly between subgroups: 93% (75/80) of those with a history of either one or two first trimester miscarriages with normal investigations and 85% (17/20) with abnormal investigations; 82% (23/28) of those with a history of recurrent miscarriages with normal investigations and 77% (10/13) with abnormal investigations; 82% (51/62) of those with a history of either one or two second trimester miscarriages with normal investigations and 85% (17/20) with abnormal investigations; 100% (9/9) with a history of recurrent second trimester miscarriages with normal investigations and 100% (6/6) with abnormal investigations. The incidence of miscarriage (11%), delivery before 37 weeks gestation (10%), or birthweight below the 5th centile (3%) in

Table 2. Results of selected investigations in women with repeated or recurrent miscarriages. Figures are proportions of those tested with abnormal results.

	First trimester miscarriages		Second trimester miscarriages	
	Repeated (2)	Recurrent (≥3)	Repeated (2)	Recurrent (≥3)
Serum folate	7/113	4/68	9/122	0/15
Serum iron	2/12	2/15	4/13	1/15
Serum ferritin	6/32	5/25	9/23	1/15
HBsAg[a]	0/14	0/10	0/17	0/5
Viral serology	2/10	2/70	3/24	1/7
Cervical cultures	–	3/28	1/15	1/8
Random blood sugar	0/3	0/10	0/32	0/4
GTT[b]	0/15	0/8	0/21	0/2
HbA1c[c]	0/2	0/23	3/9	1/2
Karyotype	3/63	6/65	5/132	1/15
Pelvic ultrasound	1/15	1/17	0/10	0/5
Hysterosalpingography	3/3	2/2	3/7	0/4
Cervical resistance studies	0/1	0/3	6/9	1/1
Lupus inhibitor	1/11	2/20	1/17	1/7
Antinuclear factor	1/6	4/16	0/10	0/6
Thyroid function tests	1/32	1/48	1/33	0/7

[a] HBsAg = Hepatitis B surface antigen.
[b] GTT = Oral glucose tolerance test.
[c] HbA1c = Haemoglobin A1c fraction.

this group was not significantly different between the subgroups.

Outcome following previous fetal abnormality

Among the 211 couples who attended the clinic for this indication, 99 (47%) of the fetal abnormalities involved structural problems (63 neural tube, 11 abdominal wall, 10 genito-urinary tract, 9 digestive tract, 6 heart). The remainder comprised 48 (23%) karyotype disorders and 64 (30%) with a variety of metabolic defects and inheritable syndromes. No other investigations were found to be of value in this group. For example, the levels of serum folate were normal in all the women who had a previous neural tube defect and did not differ from the levels in women with other previous fetal malformations.

Seventy eight (37%) couples in this category had another pregnancy after the counselling. Four pregnancies were found to be abnormal and in each case the couple elected to terminate the pregnancy.

Outcome with a chronic medical problem

Among the 240 women in this category, the most frequent problems were hypertension (77), diabetes mellitus (28), heart disease (27), renal disease (23), epilepsy (19), thyroid disease (18) and asthma (10); 38 had other medical problems. As expected, a high proportion (72%) of these women were shown to have abnormal selected investigations, usually related to the underlying disease. Almost 50% of the women referred with diabetes were found to have an abnormally high HbA1c level (>8%), indicating a need for better preconceptual diabetic control. All seven women with phenylketonuria had abnormally high phenylalaline levels, indicating a need to modify their diet before conception. Within the group with chronic hypertension several were receiving treatment with drugs considered unsuitable during pregnancy, such as angiotensin converting enzyme inhibitor or a thiazide diuretic, and some required further investigation of their hypertension. Several were, in view of their disease, advised against another pregnancy.

Of the 63 women in this category who attempted a further pregnancy following counselling, 51 (81%) had a live birth of a normal infant, a significant improvement compared with their previous live birth rate of 42% (95% CI difference 28·5–54·9%; χ^2 test: $P<0{\cdot}001$).

Discussion

Our data identify the problems likely to be encountered in a prepregnancy clinic functioning as part of the fetal medicine programme in a referral centre. The clinic is organized around the full-time appointment of a sister midwife who, in addition to initiating the process of assessment of new couples, is able to provide them with continuing support which, although difficult to evaluate, is clearly a vital function of the clinic. A further important role for the sister midwife is the discussion about contraception and the provision, when necessary, of appropriate contraceptives, at least until the assessment process is completed. An initial information gathering consultation with the sister midwife allows subsequent consultations with medical staff to be devoted much more to counselling issues. It is evident from our data that the range of problems is wide and multidisciplinary links are necessary to provide high quality information to couples. Close liaison with a clinical geneticist is essential, preferably in the prepregnancy clinic. Contact with other medical specialists (except perhaps a diabetologist) need not be so formal. We found initial communication by writing (often to the woman's own physician) to be a rewarding first step, rather than having a medical presence in the clinic.

Apart from those with recurrent second trimester miscarriages or complex medical problems, the impact of prepregnancy care is difficult to assess from our data. There is however, increasing recognition of the adverse psychological sequelae of first trimester miscarriages. Although investigations were rarely helpful, the support and counselling such a clinic can offer should not be underestimated (Turner *et al.* 1991) and encouragement can be gained from the likelihood of subsequent success (Stirrat 1990).

The previous delivery of an abnormal baby is a cause of considerable anxiety in those considering a further pregnancy. Two principal questions arise, namely· the risk of recurrence and the feasibility of prenatal diagnosis in a subsequent pregnancy. The answers depend on an accurate diagnosis of the previous abnormality. Occasionally, where the abnormality is complex, or part of a syndrome with a high recurrence risk, specialist genetic counselling is indicated. Adverse outcome in a subsequent pregnancy is not uncommon, so there is a need too for continuity between the prepregnancy clinic and subsequent antenatal care.

The value of prepregnancy counselling for couples with chronic medical disorders is evident from our data. There is an opportunity to assess and stabilize the medical condition before pregnancy, often in conjunction with a physician. This was particularly evident for diabetes mellitus, and there is now evidence that good periconceptual diabetic control will reduce the incidence of fetal abnormality and spontaneous miscarriage (Steel *et al.* 1990). Hypertension was another condition in which additional investigations of change in therapy were commonly required and in a small minority it was considered that pregnancy was contraindicated. Indeed, the gentle discouragement of a further pregnancy in some cases is undoubtedly responsible for some of the apparent improvement in outcome in this group. Other medical conditions, such as epilepsy, many have been treated with drugs inappropriate for use in pregnancy, although the effective treatment of the underlying condition must always be weighed against any possible adverse effect on pregnancy outcome (Brodie 1990; Hunter 1990). Such decisions are, in our experience, best made in conjunction with the appropriate physician responsible for their continuing care.

The demand for prepregnancy counselling has increased substantially: 323 new patients were seen in 1990, compared with 96 in 1985.

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OBSTETRICS

The effect of pH on release of PGE_2 from vaginal and endocervical preparations for induction of labour: an in-vitro study

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ABSTRACT

Objective To study the effect of pH and precoating with obstetric cream on the release of prostaglandin E_2 (PGE_2) from commercially available triacetin and starch based gels, lactose based vaginal tablets and sustained release hydrogel polymer pessaries in-vitro.

Design A prospective observational study.

Methods PGE_2 preparations held in dialysis bags were placed in Ringers lactate buffer and release of PGE_2 into the buffer was measured over 8–12 h by radioimmunoassay. The hydrogel polymer pessary was also assessed after precoating with obstetric cream.

Main outcome measures In-vitro PGE_2 release at pH 7·4, pH 5·4 and pH 3·4.

Results The gel preparations provided rapid and reliable release, while the lactose based vaginal tablet provided much lower release of PGE_2 with sudden and variable release occurring after 5–8 h, an effect which was enhanced at low pH. With the triacetin gel preparation, release of PGE_2 was reduced at lower pH, while the starch based gel appeared to provide optimal release at pH 5·4. The hydrogel polymer pessaries provided linear release in-vitro and this was reduced at pH 3·4. In addition, precoating the sustained release hydrogel polymer pessaries with obstetric cream virtually abolished release of PGE_2.

Conclusions As the vagina is normally acid, these results suggest that vaginal pH could influence PGE_2 release and this may result in variable clinical responses. In view of this, pH should be taken into account in the development of preparations for clinical use. Furthermore, the use of obstetric cream should be avoided when administering PGE_2 preparations for induction of labour.

Prostaglandin E_2 (PGE_2) is widely employed for cervical ripening and induction of labour. A variety of routes of administration and vehicles exist. The vaginal and endocervical routes appear to be the most popular because of their efficacy combined with ease of administration and low incidence of side-effects. The most widely used commercially available preparations in Europe are the triacetin based gels administered either vaginally or endocervically (Prostin Gel and Prepidil respectively; Upjohn), the lactose based vaginal tablet (Prostin Tablet; Upjohn), and the starch based gel (Cerviprost; Organon). Recently a sustained release hydrogel polymer pessary (Controlled Therapeutics) has been assessed and was marketed as Propess (Roussel Laboratories Limited) in the UK. We have previously reported changes in plasma prostaglandin metabolites in-vivo following administration of 1 mg of PGE_2 triacetin-based vaginal gel (Upjohn) and the 3 mg of PGE_2 lactose-based vaginal tablet (Greer *et al.* 1990), which suggested that both preparations released PGE_2 rapidly, but that the triacetin gel provided much greater bioavailability than the tablet.

PGE_2 is an organic acid and is therefore less soluble in aqueous solution at low pH (Stehle 1982). As the vagina normally presents an acid environment with a mean pH of 4·09 (SD 0·52) at 37–42 weeks gestation (Gleeson *et al.* 1989) this could influence the availability of PGE_2 from vaginal preparations. The presence of factors such as vaginal infection will alter the normal pH of the vaginal environment being associated with a higher pH (Peeters *et al.* 1972). The aim of this study was to determine the PGE_2 release characteristics of vaginal and endocervical PGE_2 preparations in-vitro and the effect thereon of pH. In addition, as obstetric cream is commonly used when women are examined before the induction of labour or during application of a prostaglandin preparation, we studied the effect on PGE_2 release of precoating one of these preparations, the hydrogel polymer pessary, with obstetric cream.

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Subjects and methods

Four preparations were studied; 1 mg of PGE$_2$ triacetin gel (Prostin Gel; Upjohn, UK), 3 mg of PGE$_2$ lactose based vaginal tablet (Prostin Tablet; Upjohn, UK), 0·5 mg of PGE$_2$ starch-based gel (Cerviprost; Organon, UK) and the 10 mg of PGE$_2$ sustained release hydrogel polymer pessary (Controlled Therapeutics, UK). Each preparation was placed in a cellulose dialysis bag (Sigma, UK) and suspended in a flask containing 1000 ml of Ringers lactate solution maintained at 37°C in a shaking water bath (Gallenkamp, UK), kept at a constant 30 shakes/min. The experiment was performed at pH 7·4, pH 5·4 and pH 3·4 with the pH of the solution being adjusted by means of addition of hydrochloric acid and sodium hydroxide. The pH values were chosen to reflect (i) neutral pH (7·4); (ii) the pH just above which PGE$_2$ solubility changes abruptly (pH 5·4) (Stehle 1982); and (iii) a pH at the lower end of the range of vaginal pH (3·4). This covered a range of pH values from 3·4 to 7·4 spaced at equal intervals. A 5 ml aliquot of the Ringer lactate solution was taken at the following time intervals; 0 min (before the PGE$_2$ was inserted into the flask), and at 10, 20, 30, 45, 60, 120, 150, 180, 240, 300, 360, 420 and 480 min. The sustained release hydrogel preparation was sampled for a longer time period in view of its sustained release characteristics, and additional samples were taken at 540, 600, 660 and 720 min. In addition, the effect of precoating these pessaries with obstetric cream (Hibitane, ICI, UK) was also assessed (the gels were not assessed with obstetric cream as it was impossible to coat them uniformly and as release from the lactose based tablet was found to be very poor, this preparation was also not assessed with obstetric cream). PGE$_2$ was measured by radioimmunoassay of the methyloxime derivative of PGE$_2$ as described previously (Kelly *et al.* 1986, 1989). The intra-assay coefficient of variation was 12·3% and interassay coefficient of variation 13·3%. The residual PGE$_2$ content of the hydrogel polymer pessaries was measured by high performance liquid chromatography (Barras *et al.* 1988) at the end of the experiment.

Each preparation was studied three times at pH 3 4 and pH 5·4 and four times at neutral pH. The effect of pH on the release of PGE$_2$ over time was analysed for each preparation by means of a one factor analysis of covariance (Superanova programme; Abacus Concepts, California). In this analysis PGE$_2$ was the dependent variable, time was the regressor (covariate) and pH the factor studied in the statistical analysis. The interaction between time and pH was statistically significant for all preparations studied, therefore within each group the release of PGE$_2$ at each pH was compared with each of the other pH values in turn by further one factor analysis of covariance for the interaction of time and pH on PGE$_2$ concentration. The effect of precoating the hydrogel pessaries with obstetric cream was assessed by a two factor analysis of covariance to assess the interaction between precoating with obstetric cream, pH and time. In this analysis PGE$_2$ was the dependent variable, time the regressor and pH and obstetric cream the two factors studied.

Results

The results are shown in Figs. 1 and 2 and Tables 1 and 2. All four preparations produced a significant increase in PGE$_2$ concentration in the bathing fluid over time and pH had a significant effect on prostaglandin concentrations obtained over time with all four preparations (ANCOVA for interaction of time and pH: F = 6·991, *P*<0·002 for the PGE$_2$ triacetin gel, F = 9·314; *P*<0·0002 for the PGE$_2$ lactose based tablet, F = 9·437, *P*<0·0001 for the PGE$_2$ starch based gel; and F = 23·033, *P*<0·0001 for the PGE$_2$ hydrogel pessary).

However, as can be seen from the figures the pattern of release over time and the effect of pH differed between the preparations. Release of PGE$_2$ from the triacetin gel preparation was initally rapid and was reduced at low pH. With the lactose based tablet the release of PGE$_2$ was low over the first 5 h, then increased, with very variable release of PGE$_2$

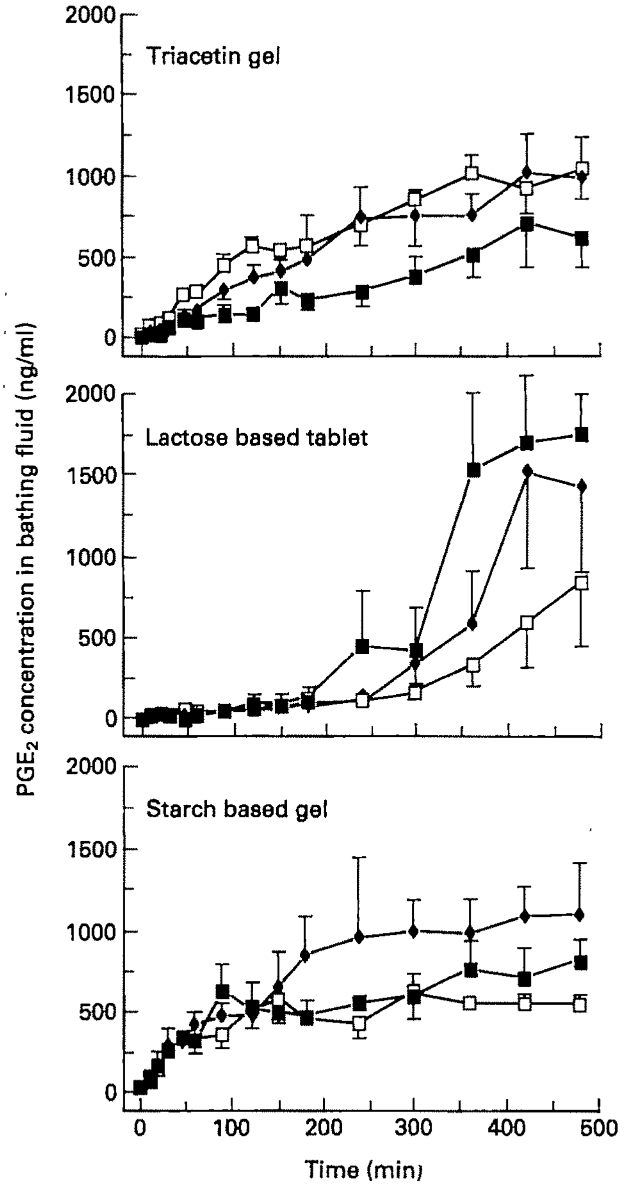

Fig. 1. Release of prostaglandin E$_2$ (PGE$_2$) over time and the effect of pH for the triacetin gel, the lactose based tablet and the starch based gel. The results are shown as mean with standard error bars. Where no error bars are visible, the standard error was too small to be apparent on the graph. □ pH 7·4; ◆ pH 5·4; ■ pH 3·4.

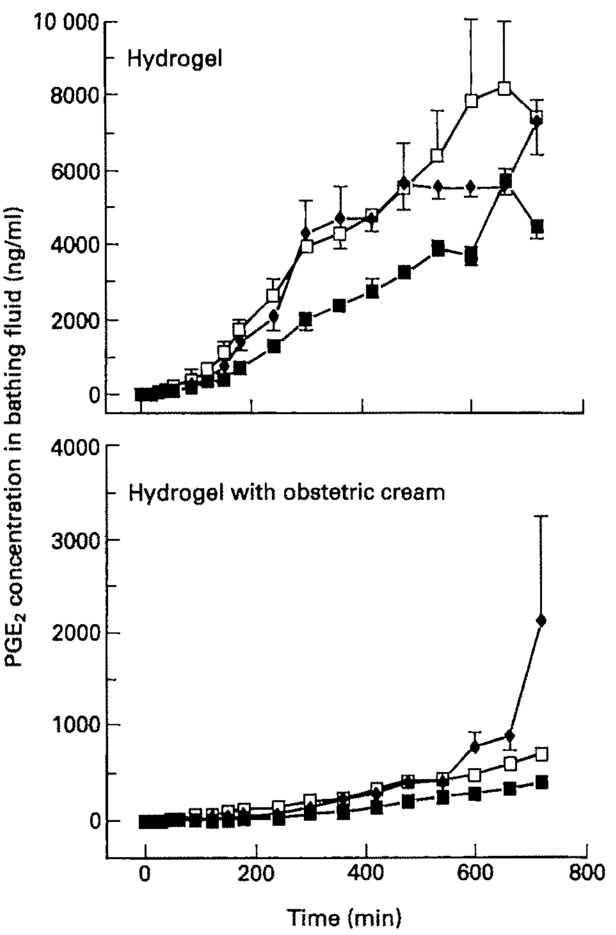

Fig. 2. Release of prostaglandin E$_2$ (PGE$_2$) over time and the effect of pH for the hydrogel pessary The results are shown as mean with standard error bars. Where no error bars are visible, the standard error was too small to be apparent on the graph. □ pH 7·4; ◆ pH 5·4; ■ pH 3·4.

between 5 and 8 h. There appeared to be increased release at low pH over the last 3 h of the experiment with the vaginal tablet. The starch-based gel preparation also provided rapid release of PGE$_2$ but maximal release occurred at pH 5·4. The sustained release hydrogel pessary provided reliable linear release over the time period studied, but the release was significantly lower at pH 3·4. A comparison between each pair of pH values within each group is shown in Table 1. Precoating the pessaries with obstetric cream virtually abolished PGE$_2$ release, at least over the first 6–7 h as seen from Fig. 2 and Table 2. (ANCOVA for interaction of precoating with obstetric cream, pH and time: F = 17·380; $P<0·0001$.)

Discussion

Although it is difficult to relate in-vitro findings to the in-vivo behaviour, the results from this study suggest that gel and hydrogel preparations provide the most reliable release of PGE$_2$ in vitro. The starch based and triacetin gels released PGE$_2$ most rapidly over the first 1–2 h. This may be because the gels provide a greater surface area and easier diffusion of PGE$_2$ out of the preparation. However, in our in-vitro model, water was present in excess and different characteristics of release may occur in-vivo where the degree of hydration may vary. The hydrogel polymer pessary provided reliable linear release over a prolonged time period. Such prolonged release may be of value for cervical ripening before induction of labour. It may also allow removal and thereby termination of further prostaglandin administration in situations such as fetal distress or uterine hypertonus, in contrast to the gel preparations which rapidly release PGE$_2$.

The effect of pH on release is also of interest. With the triacetin gel preparation and the hydrogel pessary optimal release occurred at pH 7·4. As these preparations have been used for vaginal administration, the acidity of the vagina may alter the release in-vivo and this could result in variable clinical responses. This effect of pH is unlikely to be important when this gel is used for endocervical PGE$_2$ administration as the pH will be more neutral in the cervix. These findings are in keeping with in-vivo studies where both vaginal (Greer *et al.* 1990) and endocervical (Kimball *et al.* 1986) administration resulted in rapid release of PGE$_2$ as measured by an increase in plasma PGE$_2$ metabolites. Similarly the starch based gel which is only used for endocervical administration provided rapid and reliable release at neutral pH, although release was greatest at pH 5·4. The 'bell shaped' effect of pH on PGE$_2$ release found with the starch based gel may reflect the characteristics of the vehicles behaviour rather than simply an effect of pH on PGE$_2$ solubility. However, this would also be potentially useful for vaginal administration.

The effect of pH on solubility of PGE$_2$ in aqueous solution is not unexpected as the solubility of PGE$_2$ changes abruptly around pH 5·5 from less than 5 mg/ml at pH 5·0 to 70 mg/ml at pH 5·5 (Stehle 1982). Thus, provided the vaginal pH is greater than pH 5·4 there is unlikely to be any major effect on PGE$_2$ solubility and availability. However, as the mean vaginal pH at term is 4·09 (SD 0·52) (Gleeson *et al.* 1989),

Table 1. Comparison of the effect of pH on PGE$_2$ release within each group.

	Prostaglandin E$_2$ preparation							
	Triacetin gel		Lactose based tablet		Starch based gel		Hydrogel pessary	
pH	F	*P*	F	*P*	F	*P*	F	*P*
7·4 *vs* 5·4	0·02	0·88	7·753	<0·01	15·851	<0·0001	4·362	<0·05
7·4 *vs* 3·4	11·589	<0·001	21·585	<0·0001	2·750	0·10	43·766	<0·0001
5·4 *vs* 3·4	10·407	<0·002	2·004	0·16	6·452	<0·02	30·733	<0·0001

F and *P* values computed by one-factor analysis of covariance to determine the interaction of pH and time on PGE$_2$ release.

Table 2. Residual content of prostaglandin E_2 (PGE_2) in hydrogel pessaries.

pH of solution	PGE_2 content (mg)	
	Without obstetric cream	With obstetric cream
7·4	1·08 (0·117)	8·08 (0·057)
5·4	2·00 (0·717)	7·68 (0·144)
3·4	4·50 (0·040)	8·06 (0·144)

Results are mean (SE) values.

those preparations employed vaginally are likely to provide suboptimal release under those conditions and this might explain the variable clinical responses sometimes reported. Differences in hydration and vaginal pH, the latter being associated with factors such as vaginitis, could thus explain the reduced predictability of PGE_2 release from the sustained release hydrogel pessary in-vivo compared to the in-vitro situation that we have reported previously (Johnston *et al.* 1990). It is noteworthy that the hydrogel pessary was withdrawn from the market because of adverse reactions in the form of uterine hypertonus and difficulties in removing the pessary from the vagina (Bex *et al.* 1990; Khouzam & Ledward 1990).

Precoating the sustained release hydrogel pessary with obstetric cream effectively prevented release of PGE_2 from the preparation. This is likely to occur with other preparations and, if the vagina were similarly coated from the use of such cream for examination before administration of PGE_2, poor absorption of PGE_2 might result. This might reflect the poor access to water which an obstetric cream coated preparation may have due to paraffin, a major constituent of obstetric cream, producing a waterproof coating. This is borne out by the residual PGE_2 content of the pessaries which was around 80% of the initial content after the experiment in the obstetric cream coated pessaries compared to just over 10% of the initial content in the non-coated preparations (Table 2).

The lactose-based vaginal tablet did not appear to provide a good vehicle for release of PGE_2 in-vitro in our system, with very low release rates, despite the greater PGE_2 content of these tablets compared to the gel preparations. In addition there was sudden and variable release towards the end of the 8 h observation period which was increased at low pH, and may have been due to tablet disintegration as it became saturated with water. It is unclear why the highest PGE_2 concentration occurred at low pH, but may reflect the tablet characteristics rather than PGE_2 solubility. These characteristics suggest that the lactose-based vaginal tablet may not be optimal for PGE_2 delivery as the slow release and potential for dumping of PGE_2 as the tablet disintegrates could result in a variable clinical response. These results agree with our previous findings that vaginal tablets produced substantially lower circulating levels of PGE_2 metabolites compared with the gel (Greer *et al.* 1990). Furthermore, the better clinical outcome seen in a comparative study of the 3 mg PGE_2 vaginal tablet compared with the 2 mg PGE_2 vaginal gel preparation (Mahmood 1989) could reflect the better PGE_2 bioavailability of the gel preparation.

In conclusion, these results suggest that pH can alter the release characteristics of PGE_2 from vaginal preparations and that this effect varies with the preparation. Thus, pH should be taken into account when preparations for vaginal administration are developed. The effect of pH may also, at least in part, explain some of the variable clinical responses sometimes encountered with such preparations. In addition, it should be noted that obstetric cream may inhibit release of PGE_2 as seen with the hydrogel pessary and this effect might occur with other preparations if the vagina is coated with obstetric cream. Thus, obstetric cream should be avoided for vaginal examination before induction of labour with prostaglandin preparations.

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OBSTETRICS

The efficacy of phenytoin in relation to serum levels in severe pre-eclampsia and eclampsia

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ABSTRACT

Objectives To investigate the efficacy of phenytoin in relation to total and free serum levels in patients with severe pre-eclampsia and eclampsia.
Design Prospective descriptive study.
Setting Labour Ward, King Edward VIII Hospital, Durban, South Africa. Tertiary referral centre serving an underprivileged community.
Subjects Eleven patients admitted with a hypertensive crisis. Four patients had eclampsia and 7 had impending eclampsia.
Main outcome measures Free and total phenytoin levels; efficacy of phenytoin as an anticonvulsant and side-effects of therapy.
Results Although total phenytoin levels were within the therapeutic range, free phenytoin levels were abnormally high in all patients. Three patients (2 with eclampsia and 1 with imminent eclampsia) each had a seizure after phenytoin treatment had been initiated.
Conclusion Neither total nor free phenytoin levels were good predictors of seizure control. It is postulated that the poor performance of phenytoin as an anticonvulsant in severe eclampsia may relate to inadequate distribution of the drug to the brain as a result of cerebral oedema and poor cerebral perfusion rather than paradoxical seizure activity associated with high free phenytoin levels.

Phenytoin sodium is well recognized as a specific drug for the prevention and control of seizures in epilepsy. It acts centrally, and therapeutic levels are obtained rapidly after an intravenous load. Recent studies have advocated its use in the management of eclampsia and severe pre-eclampsia (Slater 1987; Ryan 1988; Coyaji & Otio 1990; Robson 1990). However, other reports have expressed caution in the widespread use of phenytoin before proper assessment, due to its apparent lack of efficacy in preventing seizures in eclampsia (Tuffnell 1989; Dommisse 1990), although in both of the last named studies, total serum phenytoin concentrations were within the usual therapeutic range. In eclampsia because of the hypoproteinaemia, elevated free levels could be expected to be associated with these normal total values. In view of this, the present study set out to investigate the efficacy of phenytoin in relation to the serum levels achieved in patients with hypertensive crisis in pregnancy.

Subjects and methods

This study was approved by the ethics committee of the University of Natal, and was conducted in the obstetric unit of King Edward VIII Hospital, Durban, South Africa (KEH). This is a large urban tertiary referral hospital serving an underprivileged community. In 1990, 14 258 women were delivered in this unit, of whom 126 (0·9%) were admitted with eclampsia.

The study included 11 patients. All had eclampsia or impending eclampsia, i.e. hypertension and proteinuria with one of the following: persistent headaches; visual disturbances and epigastric pain; clonus and/or hyperreflexia. No patient was on phenytoin or magnesium sulphate before inclusion in the study and all patients were managed by conventional methods, which included a central venous pressure line to correct any hypovolaemia and lowering of high blood pressure with dihydralazine or nifedipine when indicated as described previously by Moodley *et al.* (1983). Prophylactic phenytoin therapy was started and the patient was delivered when she was haemodynamically stable.

Laboratory investigations

Haemoglobin, haematocrit and platelet count were measured and renal function was assessed by measurement of serum urea and electrolytes. Serum albumin levels were measured on admission and 24 h later.

Drug administration

Each patient received a loading dose of 18 mg/kg body weight of phenytoin sodium (Epanutin, Parke-Davis) diluted

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Table 1. Demographic and clinical details of patients.

Patient no.	Age (years)	Weight (kg)	Gestation (weeks)	Parity	Diagnosis	Admission BP (mmHg)	Proteinuria	GCS	No. of seizures before admission
1	30	–	36	0	Imm eclampsia	150/90	3+	15	–
2	22	89	28	0	Imm. eclampsia	200/130	3+	15	–
3*	18	81	38	0	Eclampsia	150/90	3+	15	2
4	26	65	38	0	Imm. eclampsia	190/110	4+	15	–
5*	21	68	32	2	Imm. eclampsia	180/110	4+	15	–
6	32	89	33	1	Eclampsia	170/130	4+	15	2
7	23	85	34	1	Imm. eclampsia	210/140	2+	15	–
8	23	80	36	0	Imm. eclampsia	160/120	3+	15	–
9	28	69	38	3	Eclampsia	130/190	Nil	13	1
10	21	71	36	0	Imm. eclampsia	200/140	3+	15	–
11*	32	70	32	4	Eclampsia	170/130	3+	13	3

*Indicates patients who convulsed after phenytoin. Imm. eclampsia = imminent eclampsia; GCS = Glasgow coma scale; BP = blood pressure

in 200 ml of normal saline. Patients with impending eclampsia were weighed and for the eclamptic patients, the last recorded weight at the antenatal clinic was used. No infusion pumps were available at this institution, and the loading dose was infused as an intravenous 'piggy-back arrangement' over 15–20 min as described by Earnest *et al.* (1983). Maintenance doses of 6 mg/kg body weight/day were given intravenously in four divided doses every 6 h over 24 h.

Monitoring precautions

During the infusion of phenytoin, the electrocardiogram (lead II) was monitored visually for arrhythmias. The blood pressure was measured automatically approximately every 5 min (Dynamap, Critikon Inc. Tampa, Florida). One of the authors (S.N.) was present at each infusion, and the occurrence of all side-effects was recorded

Phenytoin levels

Serial blood sampling for total and free phenytoin levels was performed by venepuncture 30 min after completion of the loading dose, then every 2 h for 6 h and then every 6 h for 24 h. A single specimen was also taken at 48 h. In addition maternal blood for phenytoin levels was drawn at delivery and cord blood samples were obtained whenever possible. Blood was spun at 2000–3000 r.p.m. for 5 min to yield serum which was stored at −18°C.

Table 2. Obstetric outcome.

Patient no	Mode of delivery	Birthweight (kg)	Neonatal outcome
1	C/S	2·7	Alive
2	NVD	1·45	FSB
3	C/S	3·35	Alive
4	C/S	3·0	Alive
5	C/S	1·75	Alive
6*	C/S	1·6/1·1	Alive/FSB
7	C/S	2·1	Alive
8	NVD	2·2	Alive
9	C/S	2·4	Alive
10	C/S	1·5	FSB
11	C/S	1·9	FSB

C/S=caesarean section, NVD=normal vaginal delivery, FSB=fresh stillbirth, *=twins.

Phenytoin assay

Total phenytoin levels. These were measured using the Cobas Mira (Roche) with reagents for the enzyme-multiplied immunoassay technique supplied by the Syva Company. Standard curves were generated weekly with a one point daily check. The co-efficient of variation for the assay was less than 10%.

Free phenytoin levels. Prior to analysis, an ultrafiltrate containing free phenytoin had been obtained using an Amicon free-level filter (Amicon Corp., Danvers, Massachusetts) and centrifuging at 25°C. Free phenytoin levels were determined using the TDX Free Phenytoin immunoassay (FPIA) method. Since the binding of phenytoin to albumin is temperature-dependent and free phenytoin was separated at 25°C, a correction factor was necessary to correct to body temperatures: Free at 37°C = 0·166 + 1·190 × Free at 25°C (Coleman *et al.* 1984).

Results

The demographic and clinical data are shown in Table 1. Two patients presented in labour and the remainder were not in labour. Four patients had eclampsia and the remainder, impending eclampsia. Three patients (two with eclampsia and one with imminent eclampsia) each had a seizure after phenytoin treatment had been initiated. These treatment failures are described below.

The obstetric outcome is shown in Table 2. The two patients admitted in labour had vaginal deliveries and the remainder were delivered by caesarean section. Eight of the 12 babies (one set of twins) were born alive and there were four fresh stillbirths. Two patients (numbers 10, 11) were diagnosed as having intrauterine deaths on admission. The other two deaths (numbers 2, 6) were related to fetal immaturity.

The phenytoin dosage regimen, maternal side-effects and serum albumin levels are shown in Table 3. Cardiovascular side-effects were hypotension ($n = 7$), tachycardia ($n = 5$) and arrhythmias ($n = 3$). Sedation was experienced by all the

Table 3. Phenytoin doses, albumin levels and maternal complications.

Patient no.	Loading dose (mg) (infusion rate) (mg/min)	Maintenance dose (mg/6 h)	Albumin levels (g/l) Hour 0	Albumin levels (g/l) Hour 24	Maternal complications
1	1200 (63)	100	N/A	N/A	Arrhythmia, sedation
2	1600 (73)	125	10	15	Nystagmus, sedation, hypotension (160/115→140/90), restlessness, disorientation)
3	1400 (100)	125	29	18	Sedation
4	1200 (30)	100	28	N/A	Arrhythmias, tachycardia (140→150), hypotension (150/90→130/64)
5	1200 (75)	100	N/A	N/A	Sedation, nausea, restlessness, tachycardia (68→126), hypotension (160/97→161/87)
6	1600 (36)	100	24	21	Sedation
7	1600 (46)	100	16	N/A	Sedation, tachycardia, hypotension (180/110→95/88)
8	1400 (47)	100	23	15	Thrombophlebitis, sedation, tachycardia
9	1200 (34)	100	21	28	Sedation, hypotension (142/87→123/69), tachycardia (110)
10	1200 (60)	100	23	13	Sedation, restlessness, tachycardia (98→158), hypotension (198/125→154/95)
11	1300 (37)	120	26	13	Sedation, arrhythmia, hypotension (177/123→124/78) (subcapsular haemorrhage)

N/A=not available

patients. Other neurological side-effects were restlessness in three patients and nystagmus in one patient. All these adverse events were transient and had no long term sequelae.

Total phenytoin levels

Immediately after termination of the initial infusion, average serum levels were 28 mg/l (17–35 mg/l). This was followed in most patients by a rapid fall off in the first 4 h to average levels of 15·1 mg/l after four further doses of 100 or 125 mg had been given serum levels were maintained at an average level of 13·4 and 12·4 mg/l at 12 h and 24 h respectively Despite no further dosing after 24 h, total serum levels averaged 11·7 mg/l in nine patients in whom 48 h levels were available (range 7·6–16·6 mg/l). Fig. 1 is a graph of total phenytoin concentrations in the three patients (3, 5 and 11) who experienced seizures after phenytoin administration. Fig. 2 shows total phenytoin concentrations in four of the patients (1, 2, 4, 7) who did not have seizures.

In most patients, the total serum phenytoin levels were within what is normally considered to be the therapeutic range of 10 to 20 mg/l for at least 24 h and in many cases for up to 48 h after the loading infusion. Total phenytoin levels at delivery in maternal and cord serum are shown in Table 4.

Free phenytoin concentrations

In people with normal albumin levels and normal renal function, the percentage of phenytoin which is unbound in the serum is consistently close to 10% at 37°C (Rall & Schleifer 1991). This equates to a therapeutic range for free phenytoin of 1 to 2 mg/l.

In all seven patients in whom free phenytoin levels were measured, the temperature corrected free levels were above 2 mg/l at all times. At certain times in some of the patients free levels were above 6 mg/l. Figs. 3 and 4 show the free phenytoin levels for the three patients who experienced seizures subsequent to phenytoin administration and for four patients who did not. Table 4 shows the free levels in maternal serum and cord serum at the time of delivery.

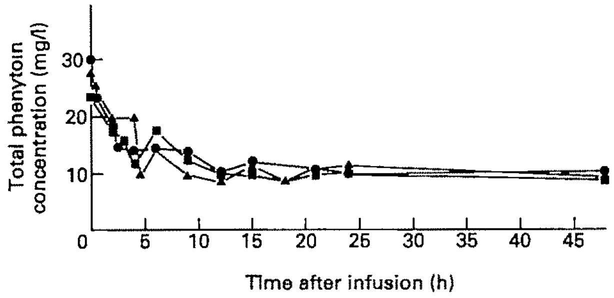

Fig. 1. Total phenytoin levels in patients who had seizures. —■—, patient 3; —●—, patient 5; —▲—, patient 11.

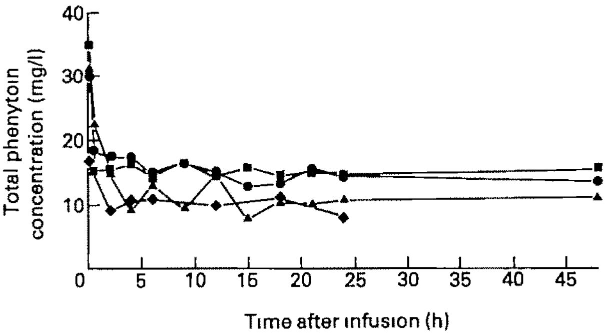

Fig. 2. Total phenytoin levels in patients who did not have seizures. —◆—, patient 1; —▲— patient 7; —●— patient, 4; —■—, patient 2.

Table 4. Free and total phenytoin concentrations and free fraction (%) at delivery in maternal and umbilical cord serum.

Patient no.	Total phenytoin (mg/l)		Free phenytoin (mg/l)		Free fraction (%)	
	Maternal	Umbilical cord	Maternal	Umbilical cord	Maternal	Umbilical cord
1	9·1	8·3	2·83	2·83	31	34
2	16·3	11·1	4·18	4·40	26	40
3	15 9	15 0	2·96	2·68	19	18
4	12·2	14·7	3·24	3·05	27	21
5	14·7	15·5	3·26	2·75	22	18
6	8·7	10·4	NA	NA	NA	NA
7	17·2	16 6	4·22	3·55	25	21
8	16·6	22 7	NA	NA	NA	NA
9	15·0	14·3	NA	NA	NA	NA
10	9·9	10 2	NA	NA	NA	NA
11	9·4	*NA	3·33	NA	35	NA

*Stillbirth.
NA = not assayed.

In all seven patients in whom free levels were measured, the percentage of phenytoin which was free was around 20% on entry and increased further during the study, in one case to over 40%. The free fraction expressed as a percentage of total phenytoin concentration in most patients fluctuated between 15 and 30% during the 48 h of the study.

In the case of patient 11, the albumin level which was 26 g/l at the start of dosing declined to 13 g/l at 24 h. The free phenytoin fraction which started at about 20%, increased after delivery (4·5 h) and reached a maximum of 48% at 9 h. This patient's free levels were above the usually recognised therapeutic range for most of the study. At the times that patients 3, 5 and 11 experienced seizures their free levels were 3·2, 4·2 and 3·7 mg/l respectively.

Description of treatment failures

Patient no. 3

An 18-year-old primigravida was admitted after two convulsions at home. On admission her blood pressure was 150/90 mmHg. She had proteinuria (3+) and was fully conscious. She had a convulsion 2 h and 15 min after an infusion of 1400 mg phenytoin given over 15 min. The maternal serum total phenytoin level was 17·4 mg/l (free phenytoin 3·2 mg/l) and her blood pressure was 150/90 mmHg at the time of the convulsion.

Patient no. 5

A 21-year-old multiparous woman was admitted with a diagnosis of imminent eclampsia. She had a blood pressure of 180/110 mmHg and proteinuria (4+). She had a convulsion 30 min after the infusion of 1200 mg phenytoin given over 15 min. The maternal serum total phenytoin level was 23·4 mg/l (free phenytoin 4·2 mg/l) and her blood pressure was 160/97 mmHg at the time of the convulsion.

Patient no. 11

A 32-year-old multiparous woman was admitted after three convulsions. She had a blood pressure of 170/130 mmHg, proteinuria (3+) and was fully conscious. She had a convulsion 21 h after the loading dose of phenytoin of 1300 mg and 3 h after an intravenous maintenance dose of 120 mg. Her blood pressure was 140/105 mmHg and the maternal serum total phenytoin level was 12·0 mg/l (free phenytoin 3·7 mg/l) at the time of the convulsion.

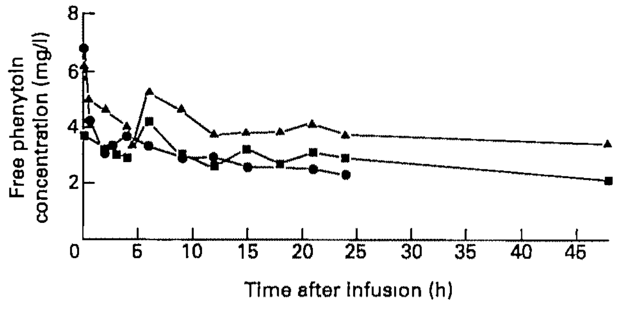

Fig. 3. Free phenytoin levels in patients who had seizures. —■—, patient 3; —●—, patient 5; —▲—, patient 11

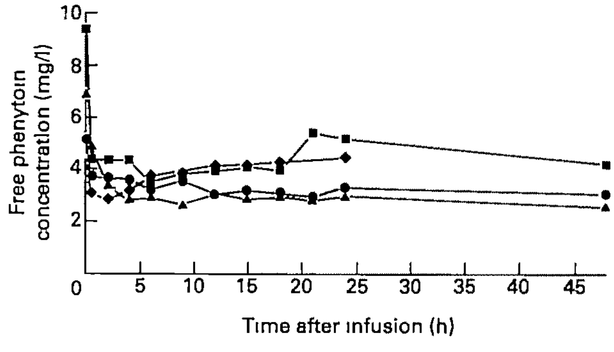

Fig. 4. Free phenytoin levels in patients who did not have seizures. —◆—, patient 1; —▲—, patient 7; —●—, patient 4; —■—, patient 2

Discussion

Although recent studies have suggested phenytoin as a useful anticonvulsant for eclampsia, its use has not been fully assessed. In a randomised study comparing phenytoin with magnesium sulphate, Dommisse (1990) reported that phenytoin sodium was not an effective anticonvulsant in 4 of 11 patients with eclampsia. In addition, Tuffnell (1989) showed that 3 of 18 patients had further convulsions despite phenytoin prophylaxis. In both studies, the treatment failures had total phenytoin serum levels within the therapeutic range and no explanation was advanced for the lack of efficacy of phenytoin in these patients. Likewise, in the present study, despite total serum concentrations within or very close to the therapeutic range, 3 of 11 patients still had seizures. Is it possible that eclamptic seizures may be more difficult to control with phenytoin than other seizures?

Eclampsia, with its profound metabolic, haemodynamic and biochemical changes may present a similar picture to that of a patient critically ill as a result of cerebral trauma. Young *et al.* (1983) found that there was no difference in the percentage of patients having seizures in the first week after head injury in a group receiving placebo and a group receiving phenytoin despite more than 78% of serum levels being over 10 mg/l. They suggest that levels of 25 to 30 mg/l are often necessary to control early seizures in this situation. In eclampsia, Coyaji & Otio (1990) have shown a relation between severity of eclampsia and serum levels of phenytoin and its anticonvulsant efficacy. In their group of mild eclamptics, two patients with levels less than 10 mg/l had convulsions, whereas levels of greater than 10 mg/l in 11 patients resulted in a 100% early seizure control. In severe eclampsia, levels of more than 10 mg/l achieved only a 40% success rate in immediate seizure control. It is interesting to note that two of three patients who had a fit during infusion in the present study had already had eclampsia before treatment.

As phenytoin is highly bound to plasma protein, it is the free fraction which is actually able to leave the plasma compartment and exert an effect. Under normal circumstances, approximately 10% of the phenytoin in the plasma is free and thus the optimal free concentration associated with seizure control is between 1 and 2 mg/l. In the present study, because of the hypoproteinaemia associated with eclampsia, free levels were much higher than normal and should have been more than sufficient for seizure control.

In fact, because the levels of 3·2, 3·7 and 4·2 mg/l recorded at the time of the fit in the three treatment failures were all above the upper limit of normal, we considered the possibility that these high free levels may have caused the seizures. In reality, the frequency of seizures as a result of phenytoin toxicity appears to be fairly low. While some authors (Stilman & Masden 1985) have suggested an incidence of about 10%, Osorio *et al.* (1989) found that the figure was much lower (about 2%). It is thus unlikely that the seizures in the present study were associated with high free phenytoin levels. In any case, free levels were equally high in the patients who did not have a fit.

It is possible, that despite adequate plasma phenytoin levels , amounts in the brain may be insufficient. Sironi *et al.* (1980) cite Sherwin *et al.* (1973) to support the possibility that seizure activity may be associated with low brain levels of phenytoin. However, Sironi *et al.* (1980), using gas chromatography to measure phenytoin levels in the brains of medically uncontrolled epileptics, found that although levels were therapeutic or greater, phenytoin was pharmacologically ineffective.

Obviously efficacy must eventually depend on how much free phenytoin gets to the site of action and therefore brain binding of phenytoin as well as regional blood flow will be important. Patients with severe eclampsia have cerebral oedema and decreased cerebral perfusion which may interfere with drug distribution in the brain, thus leading to poor control of convulsions despite high serum levels of phenytoin. On the other hand, patients with severe pre-eclampsia have little or no oedema and better cerebral perfusion and therefore phenytoin may be more effective in these patients. This hypothesis is supported by the fact that phenytoin has been less successful in severe eclamptics (Coyaji & Otio 1990; Dommisse 1990; Tuffnell *et al.* 1989; and the present study) than in mild eclamptics (Coyaji & Otio 1990), and in studies where patients were predominantly severe pre-eclamptics (Slater *et al.* 1987; Ryan *et al.* 1989, and the present study).

It is well known that individual epileptics vary in their response to phenytoin and that the so-called therapeutic range of 10 to 20 mg/l is only a guide. The present study has shown that in eclampsia, despite total levels in the therapeutic range, free levels are much higher and that neither are good predictors of seizure control.

The side-effects (hypotension, tachycardia, sedation), noted during the administration of the initial infusion, are recognised complications of administering phenytoin in small volumes at a relatively rapid rate (Earnest *et al.* 1983). No serious irreversible complications were observed. Some of these complications could probably be avoided with the use of infusion pumps where the rate could be accurately controlled.

We conclude that although high free levels of phenytoin were achieved in patients with hypertensive crisis, monitoring of neither total nor free levels is a good predictor of seizure control. It appears that phenytoin is more useful as an anticonvulsant in severe pre-eclampsia and mild eclampsia than in severe eclampsia. Lack of efficacy in the latter may be a result of altered drug distribution of phenytoin in the brain due to cerebral oedema and poor cerebral perfusion.

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OBSTETRICS

Spontaneous resolution of pre-eclampsia-related thrombocytopenia

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ABSTRACT

Objective To observe the spontaneous resolution of pre-eclampsia-related thrombocytopenia.
Design A retrospective study.
Setting High Risk Pregnancy Unit, John Radcliffe Maternity Hospital, Oxford.
Subjects Thirty women with pre-eclampsia complicated by the HELLP/ELLP syndrome who did not receive any specific treatment for their thrombocytopenia.
Intervention Serial platelet counts throughout labour and the puerperium until the platelet counts returned to levels above 100×10^9/l.
Main outcome measures Time taken from delivery and platelet nadir for platelet counts to return to levels above 100×10^9/l. The rate of recovery from the platelet nadir was measured by the slope of the serial platelet counts plotted against time.
Results The mean time until platelet count exceeded 100×10^9/l was 67 h (SD 25) after delivery and 44 h (SD 17) from the platelet nadir. All women had counts above 100×10^9/l by 111 h after delivery, and by 88 h after the platelet nadir. Although the time to recovery appeared to depend on the degree of thrombocytopenia, the rate of resolution did not.
Conclusion These data can be used as a guide by clinicians as to the expected time course for postpartum resolution of pre-eclampsia-related thrombocytopenia.

Thrombocytopenia may develop early in pre-eclampsia (Redman *et al.* 1978) and occurs in approximately 20% of pre-eclamptic patients (Burrows *et al.* 1987) although the precise incidence remains uncertain. It is probably due to increased platelet destruction secondary to vascular endothelial damage, although immune mechanisms may contribute (Burrows *et al.* 1987).

The combination of pre-eclampsia, haemolysis, elevated liver enzymes and severe thrombocytopenia has been recognised as a complication of pre-eclampsia and eclampsia for many years (Sibai 1990) and it was Weinstein (1982) who labelled the presentation with the acronym—HELLP syndrome. The haemolytic component, especially when mild, is the most difficult to detect and, when absent or undetected, patients are said to have the ELLP syndrome (Sibai 1990). Most workers have tended to consider the two syndromes together. The incidence of HELLP/ELLP among patients with pre-eclampsia has been reported as 4–12% (Sibai *et al.* 1986) but this will depend on which diagnostic criteria are used.

We have assessed the time taken after delivery to recover from severe thrombocytopenia, with an emphasis on the effect of the severity of the thrombocytopenia on duration of recovery. This retrospective study of 30 patients is related to other similar studies (Pritchard *et al.* 1976; Katz *et al.* 1990, Martin *et al.* 1990; Neiger *et al.* 1991).

Subjects and methods

We reviewed the records of patients admitted to the high risk obstetric unit with a diagnosis of pre-eclampsia from January 1989 to July 1991. The diagnosis of pre-eclampsia was based on new hypertension exceeding 140/90 mmHg and a 24-h urine protein excretion exceeding 0·5 g. In this unit, serial platelet counts are obtained on all patients with pre-eclampsia.

A total of 151 patients were admitted with pre-eclampsia, of whom 31 (20%) had or developed a platelet count below 100×10^9/l and a plasma aspartate transaminase activity greater than 40 U/l. Eighteen of the 31 had findings suggestive of haemolysis: this included red cell fragmentation in the peripheral blood film with or without either low haptoglobin levels (<0·5 g/l), lactate dehydrogenase levels greater than 600 U/l or bilirubin levels exceeding 17 µmol/l. Of the remaining 13 patients, five had no evidence of significant haemolysis but in the other eight this was not specifically investigated.

In these patients with the HELLP/ELLP syndrome, serial platelet counts were also obtained throughout labour and the puerperium. During the acute phase, when platelet counts were falling, the counts were repeated every 4 h. Once the platelet count started to rise, it was monitored every 12–24 h.

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The data were analysed statistically by linear regression and Wilcoxon rank-sum test, where appropriate. The rate of recovery from the lowest platelet reading was measured by the slope of the serial platelet counts plotted against time, using a method described previously (Matthews *et al.* 1990). P value $<0{\cdot}05$ was considered to be statistically significant.

Results

The ages of the 31 patients included in the study ranged from 18 to 37 years (mean 27·6, SD 5·2). Twenty-two (71%) were primigravid and 27 (87%) were nulliparous. The gravidity and parity of the remainder ranged from 2 to 6, and 1 to 2 respectively. The mean gestational age at delivery was 34·3 weeks (SD 4·9; range 22–42). Eleven were delivered vaginally and 20 by caesarean section.

The mean number of platelet counts on each patient was 9 (SD 3·3; range 4–18). The nadir of the platelet count averaged 52 × 10^9/l (SD 19; range 15–96 × 10^9/l). In 13 women (42%) the platelet count fell below 50 × 10^9/l. The median of the highest aspartate transaminase (AST) value was 575 U/l (range 46–2208; normal range 15–40). As expected, there was an inverse correlation between the peak AST and the nadir of the platelet count ($r = -0{\cdot}60$; $P<0{\cdot}001$). This merely reflects the well known association of thrombocytopenia with liver disturbances in pre-eclampsia.

One patient with a platelet count of 34 × 10^9/l required platelet transfusion before caesarean section. This patient was excluded from subsequent analyses.

The remaining 30 patients did not receive platelet transfusions or other specific treatment for the thrombocytopenia. Twenty-six reached the nadir of the platelet count at a mean of 27 h (SD 17; range 8–69) after delivery and four reached their nadir at 19, 10, 4 and 3 h before delivery. The lowest count was 15 × 10^9/l and none of the women suffered a haemorrhagic complication.

The mean time from delivery to resolution of thrombocytopenia, i.e. the time when the platelet count reached 100 × 10^9/l, was 67 h (SD 25; range 14–111). All the women had counts above 100 × 10^9/l within 111 h (Table 1, Fig. 1). In fact, all patients had counts above 100 × 10^9/l by 100 h after delivery except one whose recovery was complete only after 111 h. In this patient, the HELLP syndrome developed late on the third postpartum day and the nadir and recovery of the platelet count was thereby delayed to 69 and 111 h after delivery, respectively.

Table 1. Interval from delivery until platelet count reached 100 × 10^9/l

Interval (h)	No. of patients
11– 20	1
21– 30	1
31– 40	4
41– 50	2
51– 60	4
61– 70	5
71– 80	3
81– 90	4
91–100	5
101–110	0
111–120	1
Total	30

The lower the platelet count fell, the longer was the recovery time ($r = -0{\cdot}40$; $P<0{\cdot}05$) (Fig. 2). The mean time from the platelet nadir to recovery was 44 h (SD 17; range 13–18) (Fig. 1). In the patient with late onset HELLP syndrome, the platelet count recovered in 42 h which was not significantly different from the group as a whole.

The nadir of platelet counts of 12 women was below 50 × 10^9/l (mean 35, SD 9) and those of the other 18 ranged from 50 to 96 × 10^9/l (mean 65, SD 15). The rate of recovery of thrombocytopenia from the lowest point was assessed for each patient by calculating the slope of the recovery curve, estimated by simple linear regression (Matthews *et al.* 1990). The mean recovery rate for patients with a platelet nadir below 50 × 10^9/l (mean 1·9, SD 0·5) was no different from the mean recovery rate for patients with a platelet nadir ranging from 50 to 96 × 10^9/l (mean 1·7, SD 1·3) (Wilcoxon rank-sum test, sum of ranks = 228, $P = 0{\cdot}07$).

The platelet recovery rates for all 30 patients are shown in Fig. 3. As the recovery rate was linear, and for simplicity, only the starting and end points have been plotted for each case. The rate of recovery does not appear to be related to the degree of thrombocytopenia.

In 23 patients, the platelet counts were discontinued once their counts exceeded 100 × 10^9/l. In seven women, additional platelet counts were performed as their counts exceeded 400 × 10^9/l. All seven had a rebound phenomenon with platelet counts reaching values of 402–873 × 10^9/l (mean 685). It is interesting that five of these seven women had a lowest platelet count below 50 × 10^9/l. None of these women suffered a thromboembolic event and all had platelet counts of less than 400 × 10^9/l at 6 weeks after delivery.

Discussion

Pre-eclampsia remains the leading cause of maternal mortality in the United Kingdom (Department of Health 1991) and an important cause of perinatal morbidity and mortality. Although characterised by an elevation of the systemic blood pressure and proteinuria, the disease affects multiple organ systems and a subset of women may manifest the HELLP/ELLP syndrome which is associated with a poor maternal-perinatal outcome (Sibai *et al.* 1986).

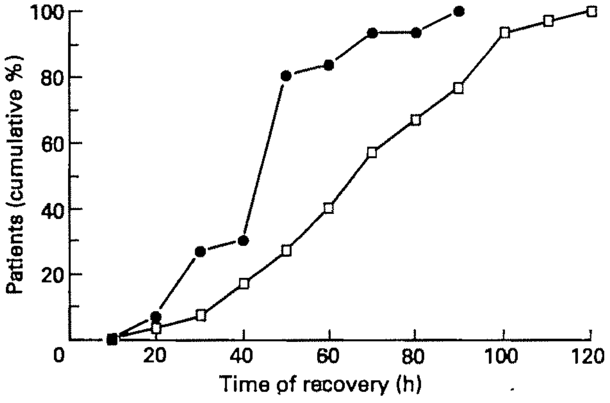

Fig. 1. Time from delivery (—□—) and time from platelet nadir (—●—) until platelet count reached 100 × 10^9/l.

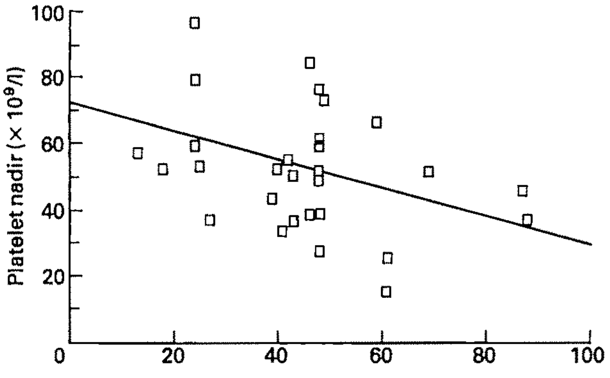

Fig. 2. Relation between platelet nadir and the recovery time from the platelet nadir until platelet count reached 100 × 10^9/l (linear correlation coefficient = −0·40; $P<0{\cdot}05$).

The true incidence of the HELLP/ELLP syndrome is unknown because of the difficulties in making the diagnosis and differences in the diagnostic criteria used (Goodlin 1976; Sibai 1990). In this study it affected 20% of patients with pre-eclampsia. This is much higher than the 4–12% incidence quoted in other series (Sibai *et al.* 1986), almost certainly owing to the fact that only complicated cases of severe pre-eclampsia/eclampsia were referred to our unit.

The reports of the resolution of pre-eclampsia-related thrombocytopenia have emanated from the United States (Pritchard *et al.* 1976, Katz *et al.* 1990, Martin *et al.* 1990; Neiger *et al.* 1991). These are represented in Table 2 together with our own results. We found that the nadir of the platelet counts occurred at a mean of 27 h postpartum. The mean time until platelet counts exceeded 100 × 10^9/l was 67 h after delivery and 44 h from the platelet nadir. Our results are comparable with the mean of 29 h to reach the nadir and 60 h to recover from delivery reported by Neiger *et al.* (1991). They did not, however, mention the time course of resolution from the platelet nadir.

Our results also suggest that although the depth of the platelet nadir is inversely related to the duration of recovery from the thrombocytopenia, the rate of resolution appears to be unaffected. In contrast, Neiger *et al.* (1991) suggest that the rate of recovery is slower among patients with the most extreme thrombocytopenia. They, however, compared groups cross-sectionally, a method which is said to be flawed statistically when analysing serial measurements (Matthews *et al.* 1990). According to our analysis, the longer time for recovery in patients with a platelet nadir below 50 × 10^9/l seems to be only a function of the greater drop in the platelet count in this group. These data on the rate of resolution, however, should be interpreted with some caution as the number of patients involved is small.

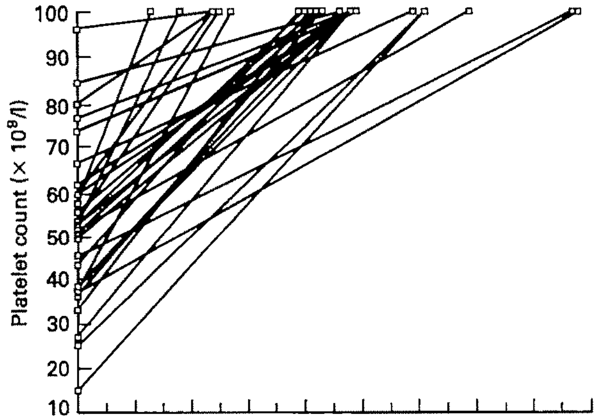

Fig. 3. Individual rates of recovery from platelet nadir until counts reached 100 × 10^9/l (only starting and end points have been plotted for each patient).

Table 2. Resolution of pre-eclampsia-related thrombocytopenia: comparison between five different series.

Series	Entry criteria	No. with platelet count <100 × 10^9/l	Resolution* (h)
Pritchard *et al.* (1976)	Eclampsia	16	120
Katz *et al.* (1990)	Pre-eclampsia	61	96
Martin *et al.* (1990)	HELLP/ELLP	158	144†
Neiger *et al.* (1991)	HELLP/ELLP	25	95‡
Present study	HELLP/ELLP	31	111§

* Time taken from delivery for platelet counts in all patients to reach 100 × 10^9/l (150 × 10^9/l in the first series).

† Excluding 11 patients who had plasma exchange.

‡ Excluding 6 patients who had platelet transfusions.

§ Excluding 1 patient who had platelet transfusion.

Recently, a patient with postpartum eclampsia was reported (Fox *et al.* 1991) in whom prostacyclin infusion was started as the thrombocytopenia had not shown signs of resolving on the second postpartum day. Our results confirm other reports (Katz *et al.* 1990; Martin *et al.* 1991; Neiger *et al.* 1991) that this is the normal course of events and spontaneous recovery of the thrombocytopenia is the rule with supportive therapy.

The rebound thrombocytosis observed in seven of our patients has been reported before (Pritchard *et al.* 1976; Neiger *et al.* 1991). The reason for this rebound phenomenon is not clear. Although the seven patients in our series and the seven described by Neiger *et al.* (1991) did not suffer any thromboembolic complications, there has been a report of maternal death from carotid artery thrombosis where the reactive thrombocytosis following a HELLP syndrome was believed to be contributory (Katz & Cefalo 1989). If this relation can be confirmed, anti-platelet therapy with low dose aspirin might be considered as prophylaxis in such patients.

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OBSTETRICS

Pre-eclampsia and trisomy 13

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ABSTRACT

Objective To assess the reported association between field trisomy 13 and maternal pre-eclampsia.

Design A retrospective case-control study.

Subjects Twenty-five women who gave birth to trisomy 13 infants in southwest England between 1971 and 1989; 38 women who gave birth to trisomy 18 infants in the same region over the same time and 50 women with normal karyotype infants matched for age, parity, and date of delivery with the trisomy 13 group.

Main outcome measures The medical records of all the women in the three groups were analysed for evidence of pre-eclampsia. Four different thresholds of pre-eclampsia were used. The incidence of pre-eclampsia was compared between the three study groups and analysed separately for primigravid and multigravid women.

Results The incidence of pre-eclampsia in pregnancies complicated by trisomy 13 was significantly higher than the incidence in the trisomy 18 and the normal karyotype control groups. This association was more pronounced in primigravid pregnancies.

Conclusions This, the largest survey of trisomy 13 and pre-eclampsia to date, suggests an association between the two conditions. It also supports the argument for a fetal factor in the pathogenesis of pre-eclampsia. We speculate on how genes encoded on chromosome 13 may be responsible.

An association between fetal trisomy 13 and the development of maternal pre-eclampsia was reported by Boyd *et al.* (1987) and this was followed by three letters in the *Lancet* reporting similar findings (Thornton *et al.* 1987; Bower *et al.* 1987; Sullivan 1987). However, these four reports presented only 33 pregnancies with trisomy 13. Furthermore, the only controlled study was by Boyd *et al.* (1987) who reported a series of 14 pregnancies with trisomy 13 and noted that all five nulliparous women developed proteinuric pre-eclampsia compared with none in the control group. Thornton *et al.* (1987) and Bower *et al.* (1987) each had nine pregnancies with trisomy 13 available for analysis and compared the incidence of pre-eclampsia with the predicted population incidence.

The aim of the present study was to record the association between maternal pre-eclampsia and trisomy 13 in a larger sample identified in the southwest of England, and to compare this with the incidence of pre-eclampsia in women giving birth to infants with trisomy 18, and in women of comparable age and parity giving birth to infants with a normal karyotype.

Subjects and methods

Identification of trisomic infants

The Regional Cytogenetics Centre, Southmead Hospital, Bristol performs karyotype analysis for the southwest of England. All pregnancies with trisomy 13 and 18 identified at the laboratory after 20 weeks of gestation were considered. Between 1971 and 1989, 41 pregnancies with trisomy 13 and 56 with trisomy 18 were identified. Of the pregnancies with trisomy 13, five were due to an unbalanced translocation. Obstetric notes were available and suitable for analysis for 25 (61%) of the 41 women who gave birth to a trisomy 13 infant and for 38 (68%) of the 56 women who gave birth to a trisomy 18 infant. Pregnancy details were obtained, including the booking and the highest recorded antenatal blood pressure, the presence of proteinuria, intrauterine growth retardation, coagulation and/or liver function test abnormality, pre-existing hypertension, renal disease and relevant family history. It was not possible to ascertain if there were any significant differences between the women whose notes were available and those where they were not available. For each trisomy 13 pregnancy, two pregnancies with karyotypically normal infants were also identified. They were selected by matching for maternal age (to within the same 5-year age range), gravidity (either primigravid or multigravid) and date of delivery (to the same month of that year).

Diagnosis of pre-eclampsia

The results were analysed using the following four alternative definitions of pre-eclampsia in order to assess any association between trisomy 13 and pre-eclampsia of dif-

Table 1. Age distribution and parity in the three study groups.

Maternal age (years)	Trisomy 13 (*n* = 25)		Trisomy 18 (*n* = 38)		Normal karyotype (*n* = 50)	
	n	(%)	*n*	(%)	*n*	(%)
<20	0	–	0	–	0	–
20–24	7	(28)	1	(3)	14	(28)
25–29	5	(20)	14	(37)	10	(20)
30–34	5	(20)	11	(30)	10	(20)
35–39	6	(24)	7	(18)	12	(24)
>39	2	(8)	5	(13)	4	(8)
Primigravid	5	(20)	14	(37)	10	(20)

fering severity. (1) Hypertension of >90 mmHg diastolic blood pressure, or an elevation of 25 mmHg diastolic blood pressure above booking value, plus proteinuria of >0·3 g per day, or '1+' or more on dip-stick testing. (2) Hypertension >100 mmHg diastolic blood pressure. (3) Hypertension >90 mmHg diastolic blood pressure. (4) A rise of diastolic blood pressure of 25 mmHg from booking.

Statistical analysis

Statistical analysis was by Fisher's exact test.

Results

General

The distribution of age and parity in the three groups is given in Table 1. The trisomy 13 group and the normal karyotype controls were matched for age, parity and date of delivery. The trisomy 18 group had a slightly higher proportion of older women and primigravida and although neither of these differences was statistically significant, the data for primigravida and multigravida were analysed separately. In the trisomy 13 group five women had a history of hypertension. All five had hypertension in a previous pregnancy, and one had a diagnosis of essential hypertension. Seven of the normal karyotype controls had a history of hypertension. Six were parous and had had hypertension in a previous pregnancy. The seventh was nulliparous with a history of essential hypertension, and a previous cerebrovascular accident. Five parous women in the trisomy 18 group had had pregnancy associated hypertension previously. None of these differences was statistically significant.

Incidence of pre-eclampsia

The incidence of pre-eclampsia in the three groups (trisomy 13 and 18, and the normal karyotype control) using the four definitions of pre-eclampsia is given in Tables 2 and 3. Overall there was a significantly higher incidence of pre-eclampsia, by all four definitions, in the trisomy 13 group compared with both the trisomy 18 group (Table 2), and the normal karyotype controls (Table 3), with the exception of pre-eclampsia according to definition 3 which was similar in the two trisomic groups.

When primigravida and multigravida are analysed separately, there was a significantly higher incidence of pre-eclampsia in all trisomy 13 primigravid women except for pre-eclampsia according to definition 4 which was similar in the two trisomic groups. The only statistically significant difference in the incidence of pre-eclampsia between the multigravida subgroups was a higher incidence of pre-eclampsia according to definitions 3 and 4 in the trisomy 13 groups compared with the normal karyotype groups.

Discussion

This study confirmed an association between trisomy 13 and pre-eclampsia described by Boyd *et al.* (1987). Two control groups were used. Trisomy 18 was used as a 'fetal' control group to assess the possibility that any association of pre-eclampsia and trisomy 13 was a function of a trisomic karyotype. Chromosome 18 was chosen as it is similar in size and shape to chromosome 13. Trisomy 21 was used as a control group in the original study by Boyd *et al.* (1987), but there was no increased incidence of pre-eclampsia above that of either the normal karyotype controls or trisomy 18. The second control group was selected from women giving birth to normal karyotype infants matched for age, parity and date of delivery, factors known to influence the incidence of pre-eclampsia (MacGillivray 1983). In a retrospective study of this nature, there are three possible sources of error—accuracy of identification of trisomic pregnancies, the diagnosis of pre-eclampsia, and sample basis.

The diagnosis of trisomy 13 and 18 was made by cytogenetic studies and is likely to be correct. Due to the severe nature of the abnormalities in trisomy 13 and 18, it is probable that most of the infants with trisomy 13 and 18 born alive in the southwest region were identified. It is possible, however, that some fetuses were not identified, due to failure to perform a karyotype, or inability to culture suitable material, such as that from fetal deaths.

Accuracy of clinical details and diagnosis of pre-eclampsia by retrieval of case notes, and interpretation of data retrospectively is the most likely source of error in this study. The

Table 2. Incidence of pre-eclampsia (PET) in pregnancies with trisomy 13 compared with trisomy 18.

	Trisomy 13			Trisomy 18			Significance		
Definition of PET	Primi (*n* = 5)	Multi (*n* = 20)	Total (*n* = 25)	Primi (*n* = 14)	Multi (*n* = 24)	Total (*n* = 38)	Primi	Multi	Total
(1)	3	3	6	0	1	1	0·010	NS	0·013
(2)	4	5	9	1	3	4	0·006	NS	0·017
(3)	4	7	11	2	5	7	0·018	NS	NS
(4)	3	7	10	2	2	4	NS	NS	0·003

Abbreviations Primi, primigravidae; multi, multigravidae; NS, not significant, $P > 0·05$.

Table 3. Incidence of pre-eclampsia (PET) in pregnancies with trisomy 13 compared with normal karyotype controls.

Definition of PET	Trisomy 13			Normal karyotype			Significance		
	Primi ($n = 5$)	Multi ($n = 20$)	Total ($n = 25$)	Primi ($n = 10$)	Multi ($n = 40$)	Total ($n = 50$)	Primi	Multi	Total
(1)	3	3	6	0	1	1	0·022	NS	0·003
(2)	4	5	9	0	4	4	0·003	NS	0·004
(3)	4	7	11	0	4	4	0·003	0·025	0·001
(4)	3	7	10	0	3	3	0·022	0·011	0·0005

Abbreviations: Primi, primigravidae, multi, multigravidae; NS, not significant, $P > 0{\cdot}05$

numbers were small, although larger than any of the studies reported to date. Because the incidence of trisomy 13 is low, it is difficult to obtain large numbers, even though our study covered 19 years. Only 25 of the 41 sets of case notes for pregnancies complicated by trisomy 13 could be located with sufficient information for analysis. Of these only five were first pregnancies. Inaccuracies and differences in the diagnosis of pre-eclampsia will also result in errors in statistical analysis. Difficulties in the diagnosis of pre-eclampsia have been stressed in most papers that deal with the aetiology of the disease (Chesley & Cooper 1986; Cooper & Liston 1979). Chesley & Cooper (1986) used women who had suffered from eclampsia as their index cases for follow up. Boyd *et al.* (1987) diagnosed pre-eclampsia only when there was hypertension and proteinuria. The present study has shown a significant association using several definitions of pre-eclampsia.

Sample bias is unlikely to be a major source of error in this study. The trisomy 13 and the normal karyotype control groups were matched for parity, age and date of delivery. The parity and age distribution of the trisomy 18 group (Table 1) would tend to increase their risk of developing pre-eclampsia, and yet this was still more common in the trisomy 13 group.

Of course it is still possible that the trisomy 13 group was at greater risk of developing pre-eclampsia for some other unidentified reason and unrelated to karyotype. Despite these limitations, and because most of the sources of error are more likely to obscure any association between pre-eclampsia and trisomy 13, we feel the evidence points to a true association. However, what is the nature of that association?

There is evidence for a genetic control of pre-eclampsia. Chesley & Cooper (1986); Cooper *et al.* (1988) and Cooper & Liston (1979) have all demonstrated that the frequency of inheritance closely fits a single gene recessive trait with a gene frequency of approximately 0·25. Arngrimsson *et al.* (1990) in an Icelandic population have reported similar findings with a single recessive gene frequency of 0·31, or a dominant gene frequency of 0·14 at 48% gene penetrance. However, their analysis would indicate, that it is a maternal rather than a fetal genetic abnormality which results in pre-eclampsia. This assumption is made on the basis that the incidence of pre-eclampsia is higher in the daughters (who have half the maternal genome) than in the daughters-in-law (who have none of the maternal genome), of women who have had pre-eclampsia. This conclusion is not valid unless the extra chromosome originates from either parent with an equal probability. There is evidence, however, that fetal factors play a part in the aetiology of pre-eclampsia, as there is an association with multiple pregnancy, hydatidiform mole, triploidy, and fetal hydrops. Furthermore both Jenkins *et al.* (1978) and Redman *et al.* (1978) have demonstrated an association between pre-eclampsia and HLA compatibility of the parents. Liston & Kilpatrick (1991) agree that a fetal genetic component is important, and suggest homozygous recessive compatibility of mother and fetus as a cause.

Brosens *et al.* (1972) and more recently Frusca *et al.* (1989) have demonstrated that in early placentation the trophoblast invades the maternal spiral arterioles, and replaces the endothelium and muscular coat. A second wave of trophoblastic activity occurs at about 16 weeks resulting in further invasion of the maternal vessels, resulting in arterioles which lack a muscle coat and are therefore unresponsive to vasoactive forces. This second wave of placentation fails to occur in women who develop pre-eclampsia and results in the placental vascular bed remaining unresponsive to the effects of vasospastic forces. This failure of adaptation also occurs in pregnancies complicated by intrauterine growth retardation in the absence of hypertension (Khong 1986). Placental studies of trisomy 13 pregnancies show non-specific lesions consisting primarily of hypoplasia and immaturity (Labbe 1989). This failure of development may extend to the absence of spiral arteriolar invasion, but there have been no morphological studies of the placental bed in trisomy 13 to test this hypothesis.

Another approach is to look at factors coded for on chromosome 13 to explain the association between pre-eclampsia and trisomy 13. These include clotting factors X and VII, and collagen type 4, which is found in cell basement membranes (Human Gene Mapping 1989). The association between basement membrane (which is a potent activator of both the coagulation cascade and platelets) and two important clotting factors is interesting, particularly as platelet activation or abnormal platelet sensitivity is a very early feature of pre-eclampsia (Redman 1990). Deletion of the terminal portion of chromosome 13 results in very low levels of factors VII and X, (Human Gene Mapping 10, 1989). Thus one possible mechanism whereby trisomy 13 may result in pre-eclampsia is due to high levels of coagulation factors by way of a 'genetic dose effect'. The resultant activation of the coagulation cascade may lead to local vascular endothelial damage, abnormal prostaglandin synthesis, platelet activation and consumption, and the second effects characteristic of maternal pre-eclampsia. Until more of the early pathophysiology of pre-eclampsia is understood, it will be difficult to test such theories about its association with trisomy 13;

however, our findings suggest that the development of pre-eclampsia is not solely an abnormal maternal response.

Finally, on a more immediate clinical level, this study reinforces the view (James *et al.* 1992) that in women with severe pre-eclampsia and a severely growth retarded infant, between 2 and 8% of fetuses will have a trisomy 13, and therefore fetal karyotyping should be considered before delivery. In our experience trisomy is found in at least 2% of these pregnancies, although the incidence rises with increasing growth retardation (James *et al.* 1992).

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FETAL AND NEONATAL MEDICINE

Transfer and metabolism of platelet-activating factor by fetal membranes, amnion and chorio-decidua

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ABSTRACT

Objective To determine the metabolism of ^{3}H–Platelet–activating factor (^{3}H–PAF) during transfer through human fetal membranes.

Design ^{3}H–PAF was added to the fetal side of cultured intact fetal membranes, amnion and chorio–decidua obtained from three pregnancies ending in elective caesarean section.

Main outcome measures Radioactivity was measured on both sides of the tissue, and in the tissue itself. In some experiments, the metabolism of ^{3}H–PAF was assessed by thin–layer chromatography.

Results Very little ^{3}H–PAF crossed the intact fetal membrane (<2%) during 24 h of culture. Most of the ^{3}H–PAF which accumulated in the membrane was converted to a range of metabolites in the chorio–decidua.

Conclusions These results suggest that PAF in amniotic fluid may not reach the decidua, and therefore is unlikely to be involved in the control of prostaglandin production from this tissue.

Human fetal membranes are thought to be the major source of prostaglandins involved in the initiation of human labour (Keirse & Turnbull 1976; Okazaki *et al.* 1981), but our understanding of the control of prostaglandin production from this tissue is still incomplete. A number of studies have investigated the control of prostaglandin E2 (PGE2) production by the amnion (Bleasdale & Johnston 1984; Mitchell 1987), on the basis that PGE2 is an important factor in the early stages of labour (Nimrod *et al.* 1984), but recent work suggested that little (1–4%) of the PGE2 produced by the amnion will reach the cervix and myometrium without being metabolized by the intervening chorion (McCoshen *et al.* 1990; Roseblade *et al.* 1990). It is possible that some other signal from either the fetus or the amnion may act as a signal to activate prostaglandin production by the decidua, which recent results suggest may be the major source of prostaglandins during labour (Helmig *et al* 1990; Khan *et al.* 1991). Platelet-activating factor (PAF) is produced from maturing fetal lung (Johnston *et al.* 1987), and has been found in increased levels in amniotic fluid during normal term labour (Hoffman *et al.* 1990), which suggested that this factor could be a fetal signal for the onset of labour. PAF increased prostaglandin synthesis by fetal membranes (Morris *et al.* 1992), which was consistent with the hypothesis that PAF has a role in labour, but PAF added to the fetal side had little effect on maternal PGE2 production (Morris *et al.* 1992). This was interpreted as meaning that PAF did not cross the fetal membranes but this was not determined directly. The aim of this study was to determine the transfer of PAF through the various fetal membrane components and establish whether this compound could reach the decidua or myometrium.

Methods

Fetal membranes were collected at elective caesarean sections being carried out at term for an indication other than hypertension or fetal growth retardation. Discs of intact fetal membrane were cultured as described elsewhere (Roseblade *et al.* 1990). In brief, the membranes were cultured on the ends of glass cylinders (outside diameter 14 mm) and held in place by silicone rubber rings (J. Walker & Co. Ltd., Woking, Surrey, England). Excess membrane was removed using a scalpel. Silicone rubber washers (J. Walker & Co. Ltd.) were placed on the other end of the cylinder to support the glass cylinders from the lid of a 12 place multiwell in which holes with a diameter of 24 mm had been drilled. Tissue culture medium (1.5 ml) was then added to each side of the membrane, to produce a two-compartment experimental system One compartment was in contact with the amnion (fetal side), and the other was in contact with the chorio-decidua (maternal side). The medium used Medium 199 with antibiotics (Gibco, Paisley, Scotland) with 10% heat-inactivated horse serum (Gibco) and 1% L-glutamine (Gibco). An intact multiwell lid was placed over the top of the system to maintain sterile culture conditions, and the culture system incubated at 37°C in 95% air: 5% CO_2. In all the experiments, a 24 h period of incubation was used before any further experimentation, to allow the membrane to recover from the trauma of delivery and the laboratory procedures. Cell membrane integrity was tested with diaphorase histochemical

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staining (Aldred & Cooke 1983), and this was used as an assessment of the viability of the cells in the fetal membranes (Roseblade *et al.* 1990). Triplicate experiments were made on membrane specimens from three pregnancies. The means from the experiments were compared by analysis of variance (ANOVA).

^{3}H-PAF (1-O-^{3}H-alkyl-2-acetyl-3-phosphoryl-choline (Amersham International, Aylesbury, UK)) was added at a concentration of 0·5 μCi (10^6 dpm)/well (0·2 nM) (unless otherwise stated), to the fetal side of the cultured membranes and the incubations continued for up to 48 h. The medium was removed from both sides of the membrane, and aliquots of the medium and the fetal membrane were placed in scintillation vials, and the radioactivity determined. Membrane samples were incubated with scintillation fluid for at least 16 h to solubilize the radioactivity; preliminary experiments showed that this was the appropriate incubation time. Samples for analysis by thin layer chromatography (TLC) were vortexed in 5mls of 2 : 1 chloroform : methanol, 2 ml water added, vortexed again and centrifuged at 450 × g for 10 min. The organic layer was removed and the aqueous layer extracted again with 5 ml 2 : 1 chloroform : methanol. The combined extracts were dried under a stream of N_2 gas and spotted onto a Merck silica gel 60 TLC plate in 10 μl of 2 : 1 chloroform : methanol. The plates were developed in chloroform : methanol : acetic acid : water (50 : 30 : 8 : 4) until the solvent front was 1 cm from the top of the plate, cut up into 1 cm sections and the radioactivity determined by β-scintillation counting. Standards of ^{3}H-PAF, ^{3}H-lyso-PAF and ^{3}H-arachidonic acid (all from Amersham International) were run simultaneously (Fig. 1). In addition, mono-oleyl glycerol was analysed by TLC and identified by iodine staining to migrate to 14 cm. The analysis of variance (ANOVA) was used to compare the activity detected in the intact membranes, chorio-decidua and amnion.

Results

^{3}H-PAF (0·5 μCi, equivalent to 1·1 × 10^6 dpm) was added to the amnion side of intact fetal membranes, and the distribution of radioactivity after incubation times of up to 48 h was determined. PAF accumulated in the fetal membrane (Table 1), so that after 48 h of incubation >70% of the original counts were localized to the fetal membrane and <2% of the counts had reached the medium on the decidual side of the membrane (Table 1). The total count in the membrane plus the media remained consistent (1·05 ± 0·2 × 10^6 dpm) and demonstrated that very little activity was lost by adherence to the wells even after 48 h of culture. Similar results were obtained when chorio-decidua was compared with intact fetal membrane (Table 2), whereas a larger percentage of the counts crossed the amnion at all time points from 2 to 24 h (Table 2).

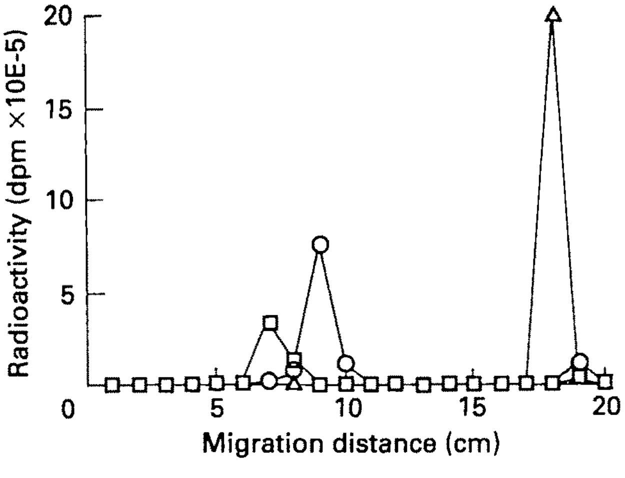

Fig. 1. Control migration of ^{3}H-PAF (○), ^{3}H-*lyso*-PAF (□) or ^{3}H-arachidonic acid (△) following separation by thin layer chromatography. Actual radioactivity scale 0–2,000,000 dpm.

The medium from the maternal side of the amnion only cultures (Table 2, column three) was analysed by TLC, and it was found that the majority of the radioactivity co-migrated with ^{3}H-PAF (Fig. 2a), which suggested that ^{3}H-PAF was not metabolized by the amnion. Tissue lipids were extracted from intact fetal membranes and from chorio-decidua after 24 h of culture, as described in the materials and methods section, and analysed by TLC. The majority of the counts co-

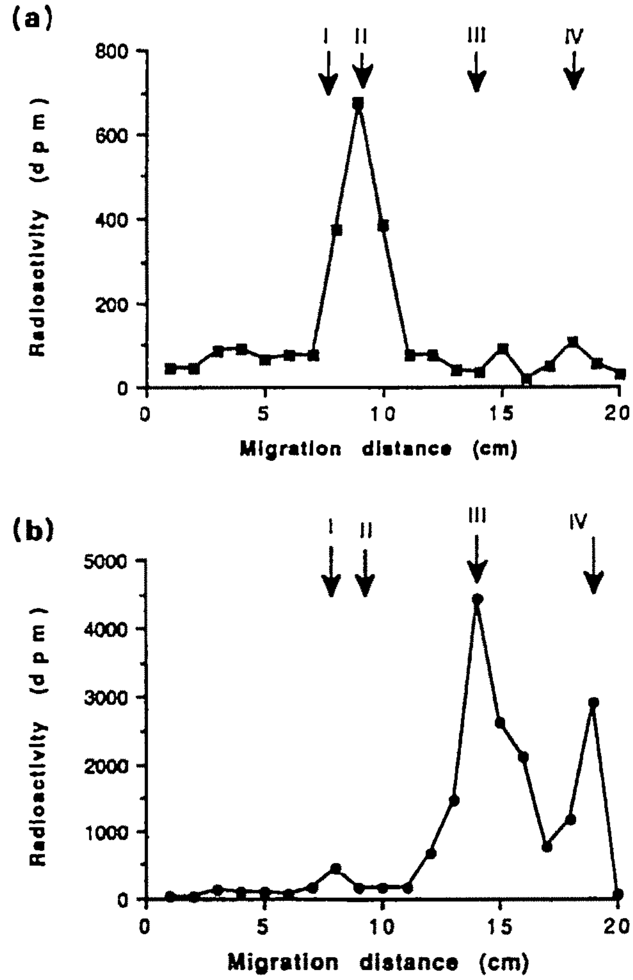

Fig. 2. Thin layer chromatography of (a) ^{3}H-PAF from the maternal side of a 24 h incubation of amnion (■) with ^{3}H-PAF added to the fetal side and (b) ^{3}H-PAF extracted from intact fetal membrane after 24 h of incubation (●) Samples were prepared as described in the methods section and are typical of three experiments. Standards are ^{3}H-*lyso*-PAF (I), ^{3}H-PAF (II), mono-acyl glycerol (III) and ^{3}H-arachidonic acid (IV).

Table 1. Distribution of ^{3}H–PAF across fetal membranes. All data are means (SEM) (n = 3) from three replicate experiments.

	Percentage of original dpm added		
Time (h)	Fetal	Membrane	Maternal
1	92·7 (8·4)	7·1 (0·5)	0·18 (0·01)
2	88·1 (5·4)	11·6 (0·9)	0·23 (0·02)
4	77·0 (2·9)	22·6 (1·5)	0·44 (0·02)
8	63·7 (2·8)	35·7 (1·7)	0·54 (0·06)
12	62·4 (8·3)	37·1 (2·1)	0·54 (0·03)
16	51·3 (1·9)	48·0 (4·0)	0·64 (0·07)
24	36·6 (1·5)	62·3 (7·0)	1·09 (0·09)
28	31·7 (2·8)	67·2 (6·2)	1·01 (0·06)
36	27·4 (2·8)	71·5 (5·8)	1·05 (0·13)
48	19·6 (2·7)	79·2 (3·9)	1·19 (0·14)

migrated with free fatty acid and mono-acyl glycerol (Fig. 2b), suggesting that extensive metabolism of the ^{3}H–PAF had occurred. These results suggest that the ^{3}H–PAF was not metabolized during transfer through the amnion but was degraded in the chorio-decidua.

Discussion

It has been suggested that PAF in amniotic fluid may be a signal for the onset of labour on the basis of (a) increased production of PGE2 from amnion cells (Morris *et al.* 1992), and (b) increased PAF concentrations in amniotic fluid during labour (Hoffman *et al.* 1990). Recent studies have implicated the decidua as a major source of prostaglandins during labour (Casey & McDonald 1988; Romero *et al.* 1988; Helmig *et al.* 1990; Khan *et al.* 1991), so the possible role of PAF in labour should be assessed in this light. This study clearly shows that although PAF accumulates in the fetal membrane, it seems to be metabolized within this tissue. This is consistent with results that have suggested that both the decidua and the chorion contain enzymes which metabolize PAF (Ban *et al.* 1986), and imply that PAF from the amniotic fluid may not have a major role in labour. This is supported by recent findings (Morris *et al.* 1992) which show that PAF added to the fetal side of intact fetal membrane had less effect on PGE2 production than PAF added to the maternal side of the membrane. Given that PAF accumulates in the chorio-decidua, and that PAF increased mainly decidual PGE2 production (Morris *et al.* 1992), it would seem that PAF from the fetal side of the tissue is most likely to be metabolized within the chorion, and does not reach the decidua as an active compound.

Table 2. ^{3}H–PAF distribution in fetal membrane, amnion and chorio-decidua. All data are means (SEM) (n = 3), from three replicate experiments Recovery of counts added averaged 94 ± 6%.

		Percentage of original dpm added		
Time (h)		Intact membrane	Chorio-decidua	Amnion
2	Fetal side	86·8 (4·6)	88·1 (2·4)	86·3 (5·4)
	Tissue	13·0 (0·3)	11·6 (1·6)	12·4 (1·4)
	Maternal side	0·2 (0·1)	0·3 (0·1)	1·3 (0·3)^a
4	Fetal side	73·0 (3·3)	75·8 (2·5)	73·5 (4·4)
	Tissue	26·6 (1·3)	23·1 (3·1)	23·3 (1·5)
	Maternal side	0·4 (0·1)	1·1 (0·2)	3·2 (0·5)^a
8	Fetal side	66·1 (5·0)	72·8 (6·0)	70·2 (5·5)
	Tissue	33·5 (3·5)	26·1 (2·8)	25·0 (2·2)
	Maternal side	0·4 (0·1)	1·1 (0·3)	4·8 (1·4)^b
17	Fetal side	47·6 (5·3)	60·6 (1·6)	51·8 (4·4)
	Tissue	51·8 (2·4)	38·2 (0·8)	42·8 (2·9)
	Maternal side	0·6 (0·1)	1·1 (0·3)	5·5 (0·9)^b
24	Fetal side	39·3 (4·8)	48·9 (3·3)	45·1 (2·2)
	Tissue	59·8 (7·9)	49·6 (2·8)	47·5 (7·4)
	Maternal side	0·9 (0·1)	1·5 (0·2)	7·4 (1·5)^b

^{a} $P<0·05$; ^{b} $P<0·01$ versus intact fetal membrane and chorio-decidua (ANOVA).

The amnion seems to act as mainly a physical barrier to the transfer of PAF through the membrane in that about 50% of the counts added to the fetal side of cultured amnion were found within the membrane within 24 h, but the PAF released from the membrane was not metabolized (Fig. 2a). These results provide one complication, since they imply that after 24 h the majority of the radioactivity in the intact fetal membrane would be in the amnion, and only a limited amount (5–10%) in the chorio-decidua. Under these conditions, most of the PAF would not be metabolized, but this is clearly not the case (Fig. 2b), so we suggest that the intact fetal membrane does not necessarily behave as the sum of its component parts, and that PAF may be transferred rapidly to the chorion within the intact membrane and metabolized there. The TLC data suggest that ^{3}H–PAF was metabolized to ^{3}H-*lyso*–PAF, ^{3}H-1-alkyl-2-acetyl-glycerol and a free fatty acid indicating enzymes other than PAF acyl-hydrolase are involved in the metabolism of PAF in the fetal membranes, but further studies are required to precisely define the hydrolysis of PAF by the chorion.

All of the studies described in this paper were carried out on fetal membranes obtained before the onset of labour. This does not exclude the possibility that the handling of PAF by fetal membranes during labour may be very different. The changes in fetal membranes during labour could lead to increased transfer of intact PAF from amniotic fluid to the decidua and myometrium, and this requires further investigation. In addition, a change in the permeability of the membranes to PAF could be an initiating factor in labour; to assess this hypothesis it will be necessary to determine the physical factors (e.g. amnion basement integrity) and biochemical factors (e.g. PAF acetyl-hydrolase) which control the transfer of intact PAF through the intact fetal membranes.

Although there are good theoretical grounds for supposing that PAF in the amniotic fluid may have a role in labour (Hoffman *et al.* 1990), the data obtained in this study and elsewhere (Morris *et al.* 1992) suggest that this is not the case and further work may be necessary to identify the fetal signal for labour.

Acknowledgments

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FETAL AND NEONATAL MEDICINE

The importance of serial biophysical assessment of fetal wellbeing in gastroschisis

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ABSTRACT

Objective To review antenatal and intrapartum assessment of pregnancies complicated by gastroschisis.
Design Retrospective descriptive study.
Setting University College Hospital, London.
Subjects 24 consecutive cases of gastroschisis between 1986 and 1991.
Results The gestational age at sonographic diagnosis was 20·3 weeks (SD 6·77) and at birth was 36·5 weeks (SD 2·06). There were 21 live births, all with good surgical outcome. There were 16 vaginal deliveries and eight caesarean sections. The elective sections were for oligohydramnios and dilated bowel (1) and clinically suspected growth retardation (1); the intrapartum caesarean sections were for fetal distress (4) and premature breech presentation (2). There were six with dilated gut on ultrasound; one of these ended in a stillbirth. There was a significant association between gut dilatation and caesarean section for fetal distress ($P = 0{\cdot}004$). There was also a significant association between meconium staining and fetal distress ($P = 0{\cdot}021$). Of these babies, 46% were ≤ third centile for corrected birth weight.
Conclusions While half of the babies with gastroschisis were small for gestational age at birth, reliable antenatal prediction of birth weight is difficult. Gut dilatation may be an indicator of either antenatal or intrapartum fetal distress, but does not correlate with poor neonatal surgical outcome. We suggest close antenatal surveillance of fetal wellbeing in all cases of gastroschisis because, in addition to growth retardation, many show some evidence of fetal distress and 12·5% end in stillbirth, even when appropriately grown.

The incidence of gastroschisis is approximately 1 in 10 000 births. In both Europe and the USA, there has been an apparent increase in incidence over the last decade. (Torfs *et al.* 1990). Unlike an omphalocoele, gastroschisis is typically an isolated abnormality with a normal karyotype. Antenatally, it can be reliably differentiated from omphalocoele by modern ultrasound. In gastroschisis, there is no sac and the umbilical vessels enter the abdominal wall normally, adjacent to the defect (Redford *et al.* 1985). As the survival rate following neonatal surgery is 85–90% (Roberts & Burge 1990; Sipes *et al.* 1990a, Stringer *et al.* 1991), an optimistic approach can be taken when counselling parents.

Since the condition of the gut is a major factor in operative success and may deteriorate towards the end of pregnancy, timing and, to a certain extent, method of delivery are important issues. Attempts have been made to correlate antenatal ultrasound findings with the condition of the intestines at birth and with eventual surgical outcome. The main features which have been suggested to indicate intestinal damage are gut dilatation and mural thickening (Bond *et al.* 1988), although neither of these were clearly defined. In fact, the original reference gives no specific definition for either of them (Nakayama *et al.* 1984). However, some authors have suggested that such findings should influence decisions regarding timing and mode of delivery (Bond *et al.* 1988) whilst others disagree (Sipes *et al.* 1990a & 1990b, Lenke *et al.* 1990). In discussing ultrasound findings, most previous studies have concentrated on structural features such as bowel morphology. Few have addressed the additional important role ultrasound can play in the serial monitoring of fetal wellbeing, although this would seem particularly pertinent, considering that a significant number of affected babies are small for gestational age at birth, with up to 77% being below the fifth centile (Carpenter *et al.* 1984).

Following two recent stillbirths of fetuses with gastroschisis in our unit, we felt that a review of our antenatal monitoring procedures of such cases was due, both in terms of the detection of fetal compromise and the timing of delivery.

Subjects and methods

A retrospective analysis of 24 consecutive cases of antenatally diagnosed gastroschisis from 1986–1991 was under-

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Table 1. Incidence of small for gestational age babies (corrected for gestational age and sex).

Birth weight centile	Patients $n = 24$	(%)
≤ 10	16	(67)
≤ 3	11	(46)
≤ 1	4	(17)

taken. Twenty were referred from other centres after the initial diagnosis. Our unit had fetal medicine, neonatal intensive care and neonatal surgical facilities available. The fetal medicine unit records, neonatal unit admission register, neonatal surgical and histopathology databases were reviewed to ensure that no cases were missed. Two therapeutic terminations of pregnancy were performed for gastroschisis at 16 weeks' gestation and were excluded from this analysis.

Details of the antenatal care and ultrasound records were analysed. No specific protocol for assessment of wellbeing in the antenatal surveillance of these fetuses was observed. Fetal morphometric measurements and ultrasonic appearance of fetal bowel were noted. As a high number of small for gestational age infants would be expected if based on abdominal circumference measurements alone, we defined small for gestational age by gestation and sex corrected birth weights less than the tenth, third, the first centiles (Thomson *et al.* 1968; Kloosterman 1970). When present, dilated bowel and mural thickening were assessed subjectively. Fetal wellbeing was assessed by cardiotocography (CTG), ultrasound amniotic fluid volume and, latterly, full biophysical profile scoring (Manning *et al.* 1985). Indications for delivery and labour ward notes were also checked. Neonatal casenotes were reviewed with respect to the outcome following surgery.

The policy of the unit regarding birth of these infants was to aim for a vaginal birth unless there was an appropriate obstetric indication for caesarean section.

Abnormal biophysical findings were defined as either a suspicious or pathological cardiotocogram (FIGO 1987) or oligohydramnios. Amniotic fluid volume was assessed both subjectively and by measurement of the largest pool (normal $> 2 \times 2$ cm) (Chamberlain *et al.* 1984) and/or the amniotic fluid index (normal > 8 cm) (Phelan *et al.* 1987). Intrapartum, they were defined as an abnormal cardiotocogram confirmed where possible by cord blood gas analysis. Where appropriate, statistical analysis was performed using the Fisher exact test (Siegel & Castellan 1989).

Results

The mean gestational age at the initial diagnosis of gastroschisis was 20·3 weeks (SD 6·77). Of the 24 subjects in this series, 14 were diagnosed by ultrasound alone, with the earliest diagnosis made at the booking scan at 11 weeks. Ten (42%) had a raised maternal serum α-feto protein at 16 weeks, and subsequently, detailed ultrasound examination noted the presence of gastroschisis and confirmed the absence of any neural tube defect. There were two cases with other abnormalities: one with arthrogryposis multiplex congenita and one with a minor hydronephrosis. There were no chromosomally abnormal babies. The male to female ratio were 1:1·4. The average gestational age at delivery was 36·5 weeks (SD 2·06); birth weight centiles are shown in Table 1. Almost half were on or below the third centile for birth weight.

Twenty-one babies (88%) are alive and well following surgery, although one of these has the associated problems of arthrogryposis. The range of follow-up is 3 months to 4 years. There were three stillbirths (Table 2).

Although fetal movements were documented on ultrasound in all cases, a formal biophysical profile scoring was recorded in only two. At the last ultrasound before birth, reduced amniotic fluid was noted in six out of 18 fetuses (33%). Umbilical Doppler studies were normal in five of the six measured. The only one with absent end diastolic velocity was the growth retarded stillbirth (case no. 22).

Dilated gut was detected on ultrasound in six (Table 3), one of which ended in a still birth (case no. 22), there were none with mural thickening. In the group with dilated gut, there were four caesarean sections: one elective caesarean section was performed because of reduced amniotic fluid volume together with the ultrasound finding of dilated bowel, and three emergency caesarean sections were for fetal distress in labour. At birth, four of these babies were on or below the third centile for birth weight and one was acidotic at birth (umbilical arterial pH 7·15, but a 5 min Apgar of 9). A good outcome following surgery was recorded in all the liveborn infants with dilated bowel and no bowel resection was required.

There were 21 cardiotocograms (CTG) available for assessment, of which 18 included antenatal recordings. There was no antenatal CTG for one of the normally grown stillbirths (case no. 23). There were seven (39%) in which the antenatal CTG was suspicious or pathological. The

Table 2. Details of three stillbirths.

Case number	Gestation at diagnosis (weeks)	Abnormal antenatal features	Gestation at fetal death (weeks)	Birth weight (centile)	Sex	Last ultrasound prior to stillbirth (days)	Findings other than gastroschisis
15	19	Fetal movements	37	90	F	4	Nil
22	16	Abnormal CTG absent end diastolic velocity dilated bowel	35	3	F	See footnote[a]	Nil
23	15	Fetal movements	34	40	F	8	Nil

[a] Case 22 was admitted for assessment for delivery; the fetus died within a few hours of the ultrasound evaluation.

Table 3. Relationship between US bowel appearance and evidence of acute on chronic fetal distress. Fisher exact test (caesarean section for fetal distress) P = 0·004.

Antenatal bowel appearance	Normal	Dilated
(n = 21 (excluding stillbirths)	n = 16	n = 5
Caesarean section for fetal distress[a]	1	3
Abnormal biophysical parameter[b]	9	4
Oligohydramnios[a]	4	2
Meconium	8	2
n = 24 (including stillbirths)	n = 18	n = 6
Abnormal CTG[a,c]	7	4
small for gestational age (≤3rd centile)	7	4
Stillbirth	2	1

[a] Defined in materials and methods.

[b] An abnormal biophysical assessment always considered of either decreased amniotic fluid volume or an abnormal CTG

[c] Antepartum and/or intrapartum.

abnormality was typically a baseline tachycardia (range 165–185 beats per min). Four of these seven had dilated herniated gut. Excluding stillbirths, eight of 17 (47%) had a pathological CTG in labour, and five of these fetuses had birth weights on or below the third centile. Two of these had fetal scalp sampling, one of which was normal and had a normal outcome; the other is mentioned below.

Twelve women (50%) went into spontaneous labour (mean gestational age 35·75 weeks (SD 1·69)), of whom six were delivered vaginally (including one assisted breech delivery at 34 weeks) and six by caesarean section. The indication for caesarean section was fetal distress in four women and premature labour with breech presentation in two. The CTG pattern of those with fetal distress was predominantly that of a tachycardia with decelerations. Two of the women in the group delivered for fetal distress had babies whose birth weights were on or below the third centile. One woman, who went into spontaneous labour at 39 weeks, developed a pathological CTG and meconium staining. She was delivered by caesarean section after a failed attempt at fetal scalp sampling. Umbilical artery pH was 7·17 with a base excess of –12 and a 5 min Apgar score of 4. Birth weight was on the 30th centile and follow-up to date is normal. One of the breech babies had a cord presentation diagnosed ultrasonically and a birth weight on the third centile Another baby had normal fetal scalp sampling to assess a pathological CTG followed by a spontaneous vaginal birth with good Apgars and birth weight on the third centile.

There were 10 (42%) inductions of labour: three for intrauterine fetal death and four for growth retardation suspected on ultrasound and/or decreased amniotic fluid volume. Labour was induced in one woman at 36 weeks for the convenience of the neonatal team. Two inductions were done at 38 and 39 weeks with no documented indication. All inductions resulted in spontaneous vaginal births. There were two elective caesarean sections; one was because of oligohydramnios and dilated bowel on ultrasound. The other section was performed at 34 weeks with poor growth given as the indication at operation; ultrasound had shown consistent growth of a small fetus with normal amniotic fluid volume and birth weight was on the tenth centile.

Amniotic fluid was meconium stained in 11 fetuses (46%). Eight of the 11 with meconium staining developed intrapartum fetal distress. Bile staining of the amniotic fluid was recorded in five. Umbilical arterial acidosis (pH<7·20) was present at birth in three of the 11 thus assessed. Two had been born by caesarean section for fetal distress.

Discussion

All cases of gastroschisis in this review were diagnosed antenatally by ultrasound. This is necessary to allow the appropriate transfer to a tertiary unit for obstetric and neonatal management. However, neonates referred for management were those suspected or diagnosed, and we are aware that, within our region, there are still cases of antenatally undiagnosed gastroschisis as well as antenatally diagnosed cases transferred postnatally, so we cannot assess exactly the overall diagnosis rate. Despite the disadvantages of postnatal transfer as discussed by Stringer *et al.* (1991), two infants required *ex utero* transfer from our unit for logistic reasons (neonatal intensive care unit full, paediatric surgeon away at time of birth).

Although maternal serum α-feto protein is useful as a screening test for gastroschisis, it is of no value in predicting affected fetuses who subsequently develop problems. It has been suggested that there is some correlation between the ultrasound appearance of bowel and subsequent intestinal damage and neonatal surgical outcome (Bond *et al.* 1988; Lenke *et al.* 1990). Our experience does not support this view, and Lenke and colleagues (1990) have shown that these bowel changes are not helpful criteria in planning delivery. In view of these inadequacies, the benefit of serial ultrasound examinations has been questioned.

Forty six per cent of infants in our review were severely small for gestational age (Table 1). This is in accord with the published literature (Carpenter *et al.* 1984; Sermer *et al.* 1987; Sipes *et al.* 1990a). When exposed to the stress of labour, these fetuses behaved predictably in that many developed meconium staining and fetal distress leading to operative birth (Laurin *et al.* 1987). While abdominal circumference measurements are the usual basis of the antenatal ultrasound diagnosis of growth retardation, their use in gastroschisis is misleading because of the herniated bowel. Our study confirms this and, therefore, raises the question of how best to identify these fetuses. The use of bony measurements such as biparietal diameter, head circumference and femur length to assess growth may be useful because the number of very small babies is nearly half. This will require further appraisal.

The majority of the reports to date have concentrated on neonatal surgical outcome and few document clearly the incidence of stillbirth and/or antenatal fetal distress. In view of the recognized association with babies being small for gestational age (46%, Table 1), one might expect a higher rate of fetal distress antenatally and even higher rate of fetal mortality. Only one previous report addresses stillbirth rate as a separate category (Lindham 1981), and although their stillbirth rate was reported as 4·7% ($n = 86$), there was also a 75% stillbirth rate in an 'indeterminate' group of anterior wall defects ($n = 28$). There were three stillbirths (12·5%) in our series which all occurred late in the third trimester. The worrying feature is that two of these babies were normally grown with no evidence of abnormal bowel morphology (Table 2), and the fetal deaths were completely unanticipated.

In our series, the presence of gut dilatation was significantly associated with caesarean section for fetal distress (Table 3). This association has not been previously reported. We suggest that this antenatal feature should alert the clinician to monitor the labour closely.

The CTG abnormalities seen were typical of the growth retarded fetus. A case report of a sinusoidal CTG associated with gastroschisis (Elliott *et al.* 1988) suggested that this may have been related to elevated levels of arginine vasopressin. We suggest that this tachycardia is more likely to be related to alterations in autonomic output due to the mechanical effect of the gut herniation.

The presence of meconium staining in labour (46%) is also in agreement with other reported series (Kirk & Wah, 1983; Sipes *et al.* 1990a). Contrary to other reports (Carpenter *et al.* 1984), we found that meconium staining was associated significantly with subsequent fetal distress ($P = 0{\cdot}021$). However, it is difficult to differentiate between meconium and bile staining, and at surgery all these babies had bile stained stomach aspirates. The association between discoloured amniotic fluid, due to meconium or bile, and fetal distress is due to the release of stomach or intestinal contents. This may be especially significant when associated with a functional obstruction due to gut dilatation.

Ultrasound provides the only reliable method of antenatal diagnosis of gastroschisis. Its usefulness in detecting changes in bowel pattern has been established, although the significance and definitions of these changes need to be clarified. It also allows serial measurement of fetal growth, and despite the difficulties with abdominal circumference measurements, plays an important role in the detection of the small for gestational age fetus. It appears, from the high incidence of fetal distress, both antepartum and intrapartum and from the high rate of stillbirths, that these fetuses, even when appropriately grown, may be less able to handle the normal stress of labour. We suggest that a further crucial role for ultrasound lies in the antenatal surveillance of fetal wellbeing in all cases of gastroschisis. Ideally, we suggest this role should be studied prospectively and comprise full biophysical profile scoring and Doppler studies on a weekly basis from 30–32 weeks onwards. This approach may help determine when delivery is indicated. Until further information is available, early delivery at 37–38 weeks may be prudent once the cervix is favourable for induction of labour.

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FETAL AND NEONATAL MEDICINE

The prognostic value of fetal ultrasonography before induction of labour

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ABSTRACT

Objective To investigate whether ultrasound examination of the fetus and amniotic fluid before induction of labour can provide useful prognostic information about the course of labour and mode of delivery.
Design A prospective observational study
Setting The delivery suite of St Mary's Hospital, London.
Subjects 101 women undergoing induction of labour.
Measured variables Biparietal diameter, head circumference, abdominal circumference, occipital position, amniotic fluid volume and umbilical artery Doppler velocimetry waveforms.
Main outcome measures The outcome of labour was assessed in terms of the induction delivery interval, the mode of delivery and the incidence of abnormal cardiotocograms in labour
Results Seven women were delivered by emergency caesarean section early in the first stage of labour because of a significant abnormality of the fetal heart trace and these pregnancies were characterized by small fetal abdominal circumference measurements. Marked oligohydramnios was also noted in five of these seven subjects. Small or average size babies who were surrounded by an adequate volume of amniotic fluid tended to be born spontaneously, whereas the majority of operative deliveries for failure to progress in labour were associated with fetal abdominal circumference measurements ≥340 mm. The mean Bishop score of women before labour who delivered spontaneously was not significantly different from the scores of women who had a forceps delivery or caesarean section. Abnormal cord Doppler waveforms were observed in only one instance.
Conclusions In women undergoing induction of labour, the measurement by ultrasonography of two variables (fetal abdominal circumference and amniotic fluid volume) may allow the prospective identification of pregnancies at increased risk of fetal distress or dystocia. If these findings can be replicated in early spontaneous labour than more rational utilization of resources may be possible in hospital based obstetric practice.

Diagnostic ultrasonography has had a major influence on obstetric practice over the past two decades. The technique has been applied primarily to the diagnosis of fetal malformation in early pregnancy and the assessment of fetal growth and well being during the third trimester. Surprisingly little research has been carried out to determine whether an ultrasound examination of the fetus during early labour may be of value in the prediction of fetal asphyxia or difficult birth. To explore this possibility, a pilot study was carried out in which an ultrasound examination was undertaken immediately before induction of labour in 101 pregnancies.

Subjects and methods

The study was approved by the hospital ethics committee and the women's consent was obtained before the examination. All 101 women had a singleton fetus with cephalic presentation. Ultrasound measurements were obtained using an ALOKA SSD-650 scanner (Aloka Co., Japan) equipped with a 3·5 MHz convex sector probe with pulsed wave Doppler facility. Fetal size was assessed by measuring abdominal circumference, head circumference and biparietal diameter using standard methodology (Neilson 1990). Occipital position was assessed by noting the position of fetal intracranial structures in relation to the maternal pelvis (Rayburn *et al.* 1989). Amniotic fluid volume was measured using the 4-quadrant technique (Phelan *et al.* 1987). Doppler waveform patterns in the umbilical vessels were recorded with the wall filter set at 100 Hz. This variable was recorded simply as the presence or absence of end-diastolic flow in the umbilical artery (Pearce & McParland 1991). Most of the scans were performed by a single observer who was not responsible for

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Table 1. Indications for induction of labour (*n*).

Gestation 42 weeks	36
Hypertension	26
Prelabour rupture of membranes	13
Maternal diabetes	4
Suspected fetal growth retardation	3
Abnormal fetal heart tracing	2
Rhesus iso-immunisation	2
Other	14
Total	100

labour ward management and the information derived from the examination was not conveyed to the labour ward staff. One exception was a case of unsuspected placenta praevia which has been excluded from the analysis.

Before induction of labour the condition of the cervix was assessed using the Bishop score (Bishop 1964). The outcome of labour was recorded with respect to the induction-delivery interval, the length of labour, the incidence of abnormal cardiotocograms during labour and the mode of delivery. If caesarean delivery was required a note was made as to whether the procedure had been performed primarily because of concern about fetal well being or primarily because of failure to progress in labour.

The 95% confidence intervals (CI) for differences in mean values and proportions were calculated using appropriate computer software (Gardner *et al.* 1989).

Results

The indications for induction of labour are listed in Table 1. Prostaglandin gel was used as the initial method of induction in 73% of cases and amniotomy with or without an intravenous infusion of oxytocin in the remainder. Forty nine per cent of the women were primiparae and the mean gestational age at induction was 40 weeks (range 33–43). The median interval between induction and delivery was 13 h (range 1–43). The median length of the first stage of labour was 4 h (range 1–27) and the median length of the second stage was 38 min (range 5–300). Mean birth weight was 3 373 g (range 1 630–4 700). Sixty women achieved a spontaneous vaginal delivery, 18 required forceps or ventouse delivery and 22 were delivered by lower segment caesarean section (the overall caesarean section rate in this unit is currently 15%). The majority of women delivered by forceps were primiparae but the parity distribution of women delivered by caesarean section was similar to that of women who delivered spontaneously. The majority of vaginal operative deliveries (11/18) were undertaken because of lack of progress in the second stage of labour.

Table 3. Occipital position on scan before induction compared with occipital position at the time of operative delivery.

	Position on scan		
Position at delivery*	OP	OT	OA
Occipito-posterior	5	—	—
Occipito-transverse	1	7	4
Occipito-anterior	—	5	13

*In another 5 cases the position of the occiput at the time of operative delivery was not recorded in the case notes.

Of the caesarean sections one was performed for cord prolapse and six were performed primarily because of cardiotocographic abnormalities early in the course of labour before the cervix was sufficiently dilated to allow fetal scalp blood sampling. The other caesarean deliveries were performed for failure to progress in labour and the mean interval between induction and delivery in these cases was 26 h. In this group significant cardiotocographic abnormalities occurred during labour in two women, but fetal scalp blood sampling did not reveal acidosis. There were no significant differences in the mean Bishop scores between women who delivered spontaneously (4·8, 95% CI 4·2–5·3), and those who required forceps (4·6, 95% CI 3·4–5·8) or caesarean section (4·3, 95% CI 3·8–4·8).

The relation between occipital position before induction and mode of delivery is shown in Table 2. There was a nonsignificant trend towards more caesarean deliveries when the occiput was posterior. Although the number of women with occipito–posterior positions is too small to allow statistical analysis, the mean abdominal circumference was less in infants born spontaneously (340 mm) than in those born by caesarean section for failure to progress (364 mm). In women who required operative delivery there was a good correlation between the position of the occiput before induction and the position at delivery (Table 3). There were several cases where an occipito–transverse position on scan was noted to be occipito–anterior at delivery (and vice versa) but there were no anomalous outcomes (such as right occipito–posterior on scan delivered as left occipito–transverse).

The abdominal circumference and biparietal diameter measurements of babies who had to be born by caesarean section for fetal distress during the first stage of labour were significantly smaller than the corresponding measurements of babies who were born spontaneously or who required caesarean section for failure to progress (Figs. 1 and 2). In only one of these cases had labour been induced primarily because of suspected intrauterine growth retardation or an abnormal fetal heart tracing. In contrast, four of the five women who had labour induced primarily for these reasons achieved a spontaneous vaginal delivery.

Table 2. Occipital position before induction and mode of delivery.

Mode of delivery	Occipito-anterior (*n* = 46)	Occipito-transverse (*n* = 40)	Occipito-posterior (*n* = 14)
Spontaneous	26 (57%)	25 (63%)	9 (64%)
Forceps	12 (26%)	6 (15%)	—
Caesarean section	8 (17%)	9 (22%)	5 (36%)

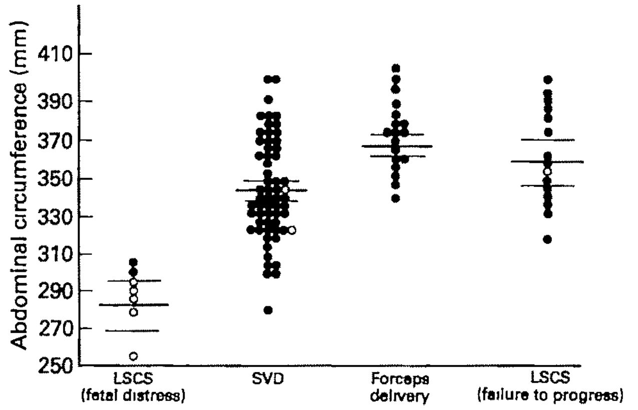

Fig. 1. Fetal abdominal circumference measurements (mm) in relation to method of delivery. The thick bars indicate the mean values for each group and the light bars represent the 95% confidence intervals (CI) for mean values. The open circles refer to cases with a 4-quadrant liquor volume <3 cm. LSCS = lower segment caesarean section; SVD = spontaneous vertex delivery; O = severe oligohydramnios

The mean abdominal circumference measurement was significantly smaller in babies born spontaneously (341 mm, 95% CI 334–348) than in those born by forceps (366 mm, 95% CI 358–375) but not significantly smaller than in those born by caesarean section for failure to progress (359 mm, 95% CI 345–372). Head measurements were, in general, less discriminating than abdominal measurements (Fig. 2) and in six cases the station of the vertex precluded the accurate measurement of the biparietal diameter.

Although smaller babies were associated with a shorter second stage of labour, fetal measurements were not useful for predicting the induction–delivery interval or the overall length of labour.

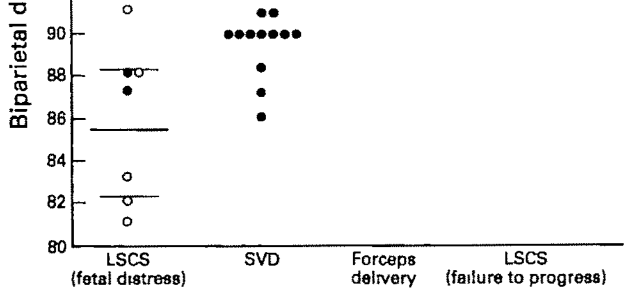

Fig. 2. Fetal biparietal diameter measurements (mm) in relation to the method of delivery. The thick bars indicate the mean values for each group and the light bars represent the 95% confidence intervals for mean values. The open circles refer to cases with a 4-quadrant liquor volume <3 cm LSCS = lower segment caesarean section; SVD = spontaneous vertex delivery; O = severe oligohydramnios.

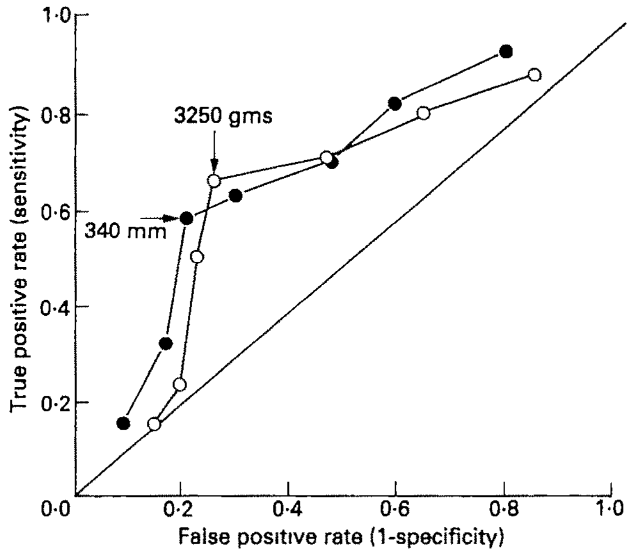

Fig. 3. Receiver operating characteristic curves comparing the ability of abdominal circumference measurements and actual birth weights to predict spontaneous delivery (true positive) as opposed to operative delivery (false positive). Cases with severe oligohydramnios have been excluded. ——●—— abdominal circumference; ——○——Birth weight.

The mean 4-quadrant amniotic fluid volume was 11·0 cm (SD 5·0). Thirty eight women were noted to have some abnormality of the fetal heart tracing during labour and in this group the mean 4-quadrant fluid volume was significantly less than in pregnancies without cardiotocographic abnormalities (8·9 versus 12·2 cm, respectively, mean difference 3·3 cm, 95% CI 1·0–5·5). In only eight women was the 4-quadrant fluid volume <3 cm and five of these babies were born by caesarean section for fetal distress.

One baby was found to have absent end diastolic flow in the umbilical artery. Oligohydramnios was also present and this baby, the smallest in the study (1 630 g at 36 weeks) was born by caesarean section because of cardiotocographic abnormality early in labour.

Figure 3 compares the receiver-operating characteristic curves of abdominal circumference measurements and birth weight when used to predict spontaneous, as opposed to operative delivery.

Discussion

The condition of the cervix before induction has long been recognized as the single most important prognostic feature determining the outcome of induced labour (Turnbull & Anderson 1968). Although failed induction of labour is seen less frequently since the introduction of prostaglandins to ripen the cervix, the need for caesarean delivery remains increased for women with a low Bishop score (Shepherd *et al.* 1979). Our observations indicate that sonographic estimates of fetal size may provide useful prognostic information about the prospects of vaginal delivery irrespective of the Bishop score: the majority of forceps or caesarean births for failure to progress were carried out for babies with an abdominal circumference >340 mm. Although ultrasound derived estimates of fetal weight are prone to occasional large errors, it would appear that abdominal circumference measurement would be as effective as actual birth weight, if it was known, for predicting the likelihood of spontaneous birth. However, fetal biometry is only one part of an equation which includes the size of the maternal pelvis. Reports of techniques combining fetal biometry with X-ray pelvimetry suggest that difficult labour can be predicted or excluded in a large proportion of cases (Morgan *et al.* 1986, 1988). These studies also suggest that abdominal measurement is more discriminating than head measurement. We do not, however, envisage that such methods will enter routine practice because of concern about fetal exposure to X-rays.

Previous reports have noted an association between oligohydramnios in late pregnancy or early labour and an increased prevalence of caesarean section for fetal distress during labour (Crowley *et al.* 1984; Rutherford *et al.* 1987) and our findings are consistent with these reports. Of eight pregnancies with marked oligohydramnios (4-quadrant amniotic fluid volume <3 cm), the smallest five babies were born for fetal distress. Perhaps the umbilical cord of a small fetus is more vulnerable to compression during uterine contractions.

The distinction between caesarean sections performed for fetal distress and those performed for failure to progress may seem arbitrary, especially as abnormal cardiotocograms are common in dysfunctional labour. There was, however, a clear difference between the two categories of caesarean section: concern about fetal well being prompted delivery of women of small babies early in the labour before failure to progress had become an issue. In contrast, the mean induction birth interval in subjects classified as failure to progress was >24 h and abnormal fetal heart rate patterns were not the primary indication for abdominal birth.

A persistent posterior position of the fetal occiput is known to be associated with difficult labour. Although we found no significant difference in the prevalence of spontaneous birth, there was a trend towards a higher rate of caesarean section for failure to progress when the position of the occiput was posterior before induction. It was, however, the larger babies that required intervention. Provided the baby is not large, occipital position in early labour may be relatively unimportant. It is possible that the occipital position during labour did not correspond to the position noted during scanning before induction, but we found good agreement between ultrasound and clinical assessments in women who ultimately required operative intervention.

Markedly abnormal umbilical cord Doppler waveforms appear to be infrequent in women screened in late pregnancy (Sarno *et al* 1989; Malcus *et al.* 1991; Pearce & McParland 1991). It is likely that placental pathology which results in abnormal velocimetry presents earlier in pregnancy with fetal growth retardation or maternal hypertension, and these pregnancies do not usually continue to term. The value of umbilical artery Doppler velocimetry for screening in late pregnancy or labour may, therefore, be limited.

If our findings can be replicated in women scanned in early spontaneous labour it may be possible to identify three separate subgroups on the basis of abdominal circumference and amniotic fluid volume measurement:

1. Small babies with reduced amniotic fluid volumes with an increased risk of intrapartum asphyxia.
2. Small or average size babies surrounded by adequate volumes of amniotic fluid with a low risk of intrapartum asphyxia or dystocia.
3. Large babies with an increased likelihood of operative delivery for failure of the labour to progress. Although this approach may seem too simplistic it has never been tested because clinical estimates of fetal size and amniotic fluid volume are notoriously inaccurate. If such a triage, with objective and reproducible ultrasound criteria, is feasible, then problems could be anticipated more accurately, and women in labour could be supervised more appropriately. The measurements proposed are simple to perform and could easily be incorporated into the concept of a labour ward admission test (Ingemarsson *et al.* 1986). This may stimulate a move away from the widely held philosophy that labour is only normal in retrospect.

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GYNAECOLOGY

Long term follow up of women after hysterectomy with a history of pre-invasive cancer of the cervix

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ABSTRACT

Objective A long term review of women after hysterectomy with a history of pre-invasive carcinoma of the cervix.

Design 193 women had cervical intra-epithelial neoplasia and two had adenocarcinoma *in situ* either at hysterectomy or at previous cone biopsy. These were followed up by annual cytology

Setting South Glamorgan Health Authority.

Subjects Of 195 women who had a hysterectomy, 143 have been followed up cytologically for more than 10 years and 43 for more than 20 years: a total of 2800 women years of experience.

Main outcome measures Timing of abnormal smears.

Results A detailed review of the five women with abnormal smears. The estimated percentage of women who remain negative is 98% at five years, 98·4%, at 10 years and 96·5% at 20 years.

Conclusion Cytological screening of all women who had a hysterectomy with a history of CIN is indicated for the first two years after hysterectomy. Thereafter the estimated incidence of 0 7 per 1000 women years is higher than the general population but it is not a sufficient reason to screen more frequently. We recommend screening for the carcinoma of the vagina to be every three years which is the same screening frequency as for cervical carcinoma in the general population.

The present policy of indefinite annual vault smears following hysterectomy for pre-invasive lesions of the cervix is based on the rationale that both pre-invasive and invasive carcinoma of the vagina have been found years after original hysterectomy (Funnell & Merrill 1963; Boyes *et al.* 1970; Creasman & Rutledge 1972; Kolstad & Klem 1976; Stuart *et al.* 1981).

Although only 0·5% of the total female genital tract lesions are pre-invasive vaginal lesions (Cramer & Cutler 1974), most authors (Funnell & Merrill 1963; Boyes *et al.* 1970; Creasman & Rutledge 1972; Kolstad & Klem 1976; McIndoe *et al.* 1984) feel that cervical pre-invasive lesions predispose to pre-invasive and invasive lesions in the vagina. The similarity of progression of both cervical and vaginal pre-invasive into invasive lesions is assumed. Some authors suggest that this similarity between the natural history of the two diseases can be explained by the theory of multicentric origin (Rutledge 1967), as the epithelium of both the vagina and the cervix arise from the urogenital sinus (Marcus 1960).

The natural history of vaginal intra-epithelial carcinoma is poorly understood; the time scale for the development of invasive vaginal carcinoma being unknown. Long term reviews of patients followed up annually are therefore of clinical importance.

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Subjects and methods

The Cardiff Cytology Study began in 1965 (Landsman *et al.* 1977). We report the follow up of 195 women who had a hysterectomy with a diagnosis of cervical intra-epithelial neoplasia (193) or adenocarcinoma *in situ* (2) made either at hysterectomy or at previous cone biopsy. None of the women had any other gynaecological malignancy. As a general policy, these were rescreened annually. One hundred and forty three have now been followed for more than 10 years, 95 for 15 years and 43 for more than 20 years. In total, there are about 2800 women years of experience.

Result

All 195 women had a hysterectomy between the years 1955–1977. Of these, 127 women underwent prior cone biopsy in the years 1962–1976. The histological diagnosis at cone biopsy and at hysterectomy is shown in Table 1 Only 35 patients had colposcopy before hysterectomy, as gynaecologists in the area did not start to refer patients for routine colposcopic examination prior to surgery for CIN till the late 1970s.

Of the 195 hysterectomies, 190 were performed by an abdominal and five by a vaginal route The interval in years between cone biopsy and hysterectomy and indication for hysterectomy is shown in Table 2. The length of cytological

Table 1. Histology of cone biopsies and hysterectomy specimens.

	Histology at hysterectomy			
Histology at cone biopsy	CIN	Benign conditions	Histology not found	Total *n*
Cone biopsy not performed	68	0	0	68
Cone biopsy				127
CIN	60	62	2	
NS	1	0	0	
AIS	1	1	0	

CIN = Cervical intra-epithelial neoplasia; AIS = Adenocarcinoma in situ; NS = not significant.

follow up in years, the times at which the five abnormal smears occurred and the length of time for which the other 190 women are definitely known to have remained negative is shown in Fig. 1. The case histories of these five women are described in detail below. The nomenclature used for abnormal smears is the same as described in the Cardiff Cervical Cytology Study (Evans *et al.* 1981).

Case summaries

Case 1. The woman had CIN 3 incompletely removed by a cone biopsy. The follow up smear at three months was suspicious of malignancy. Five months after the cone biopsy a subtotal hysterectomy was inadvertently performed, the line of resected uterus being through the cervical muscular wall. A smear performed four months after hysterectomy was suspicious of malignancy. There was no clinical tumour, the woman was not colposcoped and the vagina was not biopsied. She was treated by radiotherapy to the vagina, and follow up for eight years showed no evidence of recurrence. The woman remains well 23 years after radiotherapy.

Case 2. The woman had two cone biopsies. Both showed incomplete removal of CIN 3. Thirteen months after the second cone biopsy, the woman underwent a hysterectomy, bilateral salpingoophorectomy and removal of a vaginal cuff as the smear continued to show suspicion of malignancy. Histology of the hysterectomy specimen showed CIN 1 only. A vault smear performed four months after hysterectomy showed malignant cells. Subsequently, the woman had a vault smear every three–six months for five years; her results varied from dyskaryotic to malignant. Repeated colposcopy findings failed to show any abnormality and vault biopsy revealed chronic inflammation only. After five years the smear reverted to normal and has remained so for a further 12 years.

Case 3. A hysterectomy was performed as treatment for CIN 3. Pathology demonstrated incomplete excision. The woman's first malignant smear occurred 20 months later and a random vault biopsy of slightly red looking epithelium without colposcopic control showed vaginal intra-epithelial neoplasia with early invasion. The patient was treated with radiotherapy. She has been followed up for 27 years by annual smears which remained negative.

Case 4. A hysterectomy was performed on this patient for dysmenorrhoea two years after a cone biopsy was reported as CIN 3 with complete removal. The histology of the uterus showed no abnormality. Her annual smears were negative for 11 years. One year later a dyskaryotic smear was investigated by a colposcopy and biopsy. Vaginal intra-epithelial neoplasia Grade 2 was diagnosed, and the vaginal vault lesion was treated by laser vaporisation. Two years after the therapy the woman's smears remained negative.

Case 5. CIN 3 was found incidentally in this woman after a vaginal hysterectomy was performed for a repair for procidentia. She was followed up for three years by vault smears only which were negative. She then defaulted and presented

Table 2. Interval in years between cone biopsy and hysterectomy and indication for hysterectomy. Post cone complications = haematometra (1); bleeding after cone biopsy (1) CB = cone biopsy.

	Interval in years													
Indication for hysterectomy	no C.B	<1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12	Total *n*
Primary treatment for dysplasia	64													64
Incidental find at hysterectomy, no cone	4													4
Incomplete cone		22												22
Abnormal smear after cone		24	16	5	2		2							49
Post cone complications		2												2
Gynaecological pathology		16	4	9	3	2	4	2	4	2	2	2	1	51
Not known														3
TOTAL														195

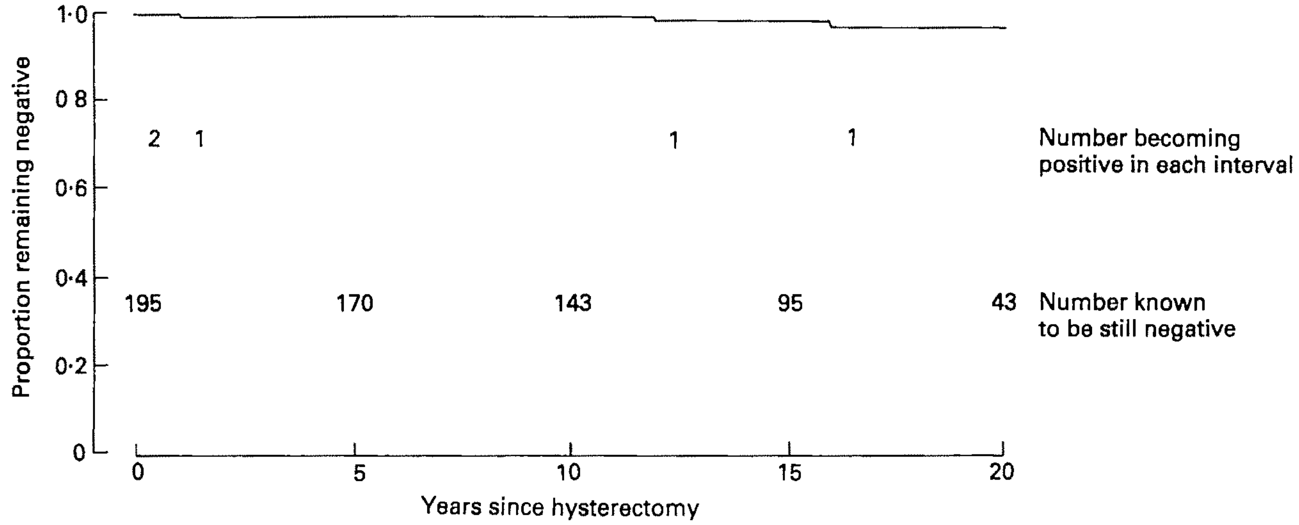

Fig. 1. Cervical cytology, outcome of screening after hysterectomy in women with CIN at hysterectomy or at previous cone biopsy.

13 years later with a clinical invasive carcinoma of her lower vagina and was treated with radiotherapy. The woman remained well for the two years of follow up but died four years after the radiotherapy at the age of 82. The cause of death is not known.

The life table (Fig. 1) showed that the estimated percentage of women who remain negative is 98·4% (95% CI 96·7%–99·9%) at 5 years; 98·4% (95% CI 96·7%–99·9%) at 10 years; 97·7% (95% CI 95·5%–99·9%) at 15 years; and 96·5% (95% CI 93·3%–99·7%) at 20 years. Thus, 1·6% of such women have developed abnormal smears within 10 years and 3·5% within 20 years.

Discussion

Of the 195 women followed up, only five women developed abnormal smears: one dyskaryotic, one suspicious of malignancy and three with malignant cells. Three smears became abnormal within the first two years (two within four months and one within 20 months) of hysterectomy This suggests that the original CIN lesion was not completely removed at hysterectomy.

In order to identify these women, it is necessary to perform vaginal cytology of all women who have a hysterectomy and a history of CIN at short intervals for at least the first two years after hysterectomy. It should be emphasised that a large part of this series relates to a period before the colposcope was available and it is possible that preoperative colposcopy might result in a reduction of the number of women by diagnosing the 4% of women in whom the transformation zone extends onto the vaginal fornix (Kolstad 1976).

What, however, should be the policy after that? There were two cases of genuine recurrence or new disease, one with vaginal intra-epithelial neoplasia grade 2 after 12 years and one with invasive carcinoma of the lower vagina 16 years after hysterectomy. Construction of a new life table to estimate the incidence of the new disease by excluding the three cases who became positive within two years of the original hysterectomy shows the estimated incidence is 0% at 10 years, 0·8% at 15 years and 2·0% at 20 years (95% CI 0·1%–4·7%). Alternatively, the estimated incidence of new disease based on two cases (one *in situ* and one invasive) in 2 800 women years of follow up is 0·7 per 1000 women years.

There are numerous difficulties comparing our results with other authors. It is impossible to be certain that the original histology of CIN is comparable between studies. Some studies consider only women with carcinoma *in situ* (Boyes *et al.* 1970; Brudenell *et al.* 1973; Creasman & Rutledge 1972; Kolstad & Klem 1976); some consider those with carcinoma *in situ* and/or severe dysplasia (Gemmell *et al.* 1990); carcinoma *in situ* and severe dysplasia (Kirkup *et al.* 1979); some, like us, consider women with any grade of CIN (Fawdry 1984). In some studies, it is impossible to differentiate betweeen the new and the persistent disease (Brudenell *et al.* 1973; Kolstad & Klem 1976; Gemmell *et al* 1990).

Estimated incidence of new disease based on women years of follow up was 0·9 per 1000 women years (Boyes *et al.* 1970), 0·3 per 1000 women years (Fawdry 1984), 0 per 1000 women years (Kirkup *et al.* 1979). None of the mentioned authors use the method of a life table analysis to estimate the incidence which we feel is the most appropriate way to analyse the data. However, given these reservations, the approximate incidence based on the reported literature is in the range of 0·5–1·0/1000 women years. A rather more doubtful guess would suggest that about half of this new disease is *in situ* and half invasive.

It could be argued that annual screening for those who remain negative for at least two years after the hysterectomy is unnecessary. Whether the screening interval should then be the same as for the general population (Kirkup *et al.* 1979; Gemmell *et al.* 1990) or shorter obviously depends on whether the rate of conversion to abnormality is higher than for the general population. The registration rate of vaginal carcinoma for the years 1983, 1984 and 1986 (HMSO 1986, 1988 and 1991) in women aged 25–74 years is between 0·7 and 0·9/100 000 women years. Our study shows the incidence at least one order of magnitude higher than the general population (given the estimated incidence in the hysterectomy group includes *in situ* disease, while the OPCS data should only contain invasive disease). However, the general population are not screened for vaginal carcinoma, but they are screened for cervical carcinoma. The risk of vaginal carcinoma after hysterectomy for pre-invasive carcinoma of the cervix is similar to the incidence of pre-invasive carcinoma of the cervix in the general population. As the screening interval should be based upon the estimate of the time taken to progress from the pre-invasive to malignant disease, and in the absence of any definite evidence that the natural history of the two diseases is different, we recommend screening for carcinoma of the vagina in this group to be at the same frequency as that for cervical carcinoma in the general population, that is, every three years.

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GYNAECOLOGY

Transcervical resection of the endometrium: a review of 400 consecutive patients

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ABSTRACT

Objective To assess the efficacy of transcervical resection of the endometrium (TCRE) in women presenting with menstrual disorders.
Design A retrospective audit of 400 patients.
Setting The Department of Gynaecology, St John's Hospital, Chelmsford, Essex.
Subjects 400 consecutive referrals with various bleeding disorders which were suitable for treatment with TCRE.
Interventions TCRE, either partially or completely.
Main outcome measures Patient satisfaction with procedure at 4 months. The procedure was initially recorded as a failure if any further therapy was required but satisfaction after a second procedure was assessed.
Results 432 procedures were performed in 400 women. Major operative complications were rare with two (0·46%) uterine perforations, four (0·93%) primary haemorrhages requiring Tamponade to control bleeding and one (0·23%) secondary haemorrhage requiring hysterectomy to control it. Glycine toxicity was not clinically apparent. 85% were satisfied after the initial TCRE and 92% were satisfied if the procedure was repeated.
Conclusion TCRE is an advance in the management of menstrual disorders. Extensive training is required to minimise complications. The lack of long term follow-up is its major deficiency but this will be rectified in the future.

Excessive menstrual bleeding is a common presenting symptom in women attending for gynaecological consultation. Conventional treatment until recently, consisting of drugs, blind sampling with metal curettage or hysterectomy, has been extended by methods to destroy the endometrium while leaving the uterus.

The use of an urological resectoscope to perform TCRE has been reported previously by several groups (Decherney *et al.* 1987; Magos *et al.* 1989; Magos *et al.* 1991; Hill & Maher 1990). The procedure is gaining popularity in this country and has financial implications for both health authorities and private insurance companies. It has major advantages for many women who are suitable for the procedure since it avoids a hysterectomy, the most common major operation performed in the reproductive years (Hill & Maher 1990).

We describe the outcome of treatment in 400 consecutive patients who underwent TCRE either partially for the treatment of local lesions or more commonly completely where the aim was to destroy most of the endometrium.

Subjects and methods

The women all attended a routine gynaecological clinic and most had been referred primarily with a menstrual disorder. Quantitative measurement of menstrual loss is difficult and time-consuming, therefore, a complaint of unacceptably heavy, prolonged or frequent menstruation sufficient to prevent the patient from leading a normal life was used as the indication for therapy.

All women were assessed with a medical and gynaecological history and an examination. Vaginal ultrasound was performed by the clinician in the clinic. Prior to endometrial resection, hysteroscopy (Hamou Micro-Hysteroscope 1, Karl Storz) and endometrial biopsy (Vabra, Suction Curette) were performed on women with irregular bleeding and on post menopausal women. Most premenopausal women who had a complete TCRE had been treated unsuccessfully with medical therapy before the decision for surgery and would have otherwise been considered for hysterectomy. Patients with uterine size greater than a 12 week pregnancy were excluded.

Information given to patients emphasised the following:

1. Amenorrhoea would probably not occur but a persistent reduction in menstrual flow was the aim.
2. There would be interference with fertility but no guarantee of sterility. Complete TCRE was offered only to women who had finished child-bearing; sterilisation (posterior colpotomy and Pomeroy's technique) quite often was performed at the same time.

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3. Post operative recovery would be rapid with minimal disruption to normal activity. There was a small possibility of trauma to the uterus during the operation which might require hysterectomy.

The procedure of TCRE was carried out on 432 occasions in 400 women between February 1989 and January 1991. Of these, 31 women had a repeat procedure and one had three procedures. All procedures were performed by one operator (LR). The mean age of the patients was 45 years (range 24–72) (Fig. 1).

Indication for therapy was heavy regular menstruation in 320 patients (80%), irregular and heavy menstruation in 65 (16%) and post menopausal bleeding, or bleeding related to hormone replacement therapy, in 15 patients (4%).

No patient was given pre-operative medical therapy to suppress the endometrium. Patients were operated on at any time in the menstrual cycle. At first they were admitted as day cases and they chose whether the procedure was performed under general or local anaesthetic (intracervical block and intravenous sedation). From May 1990, the procedure was offered to patients on an outpatient basis with the use of an intra-cervical block (8·8 ml Prilocaine hydrochloride and Octapressin administered laterally at the level of the internal os with a dental syringe and 21-gauge needle) without the use of intravenous sedation. Diathermy to the endometrium does not produce much pain so that only light anaesthesia is required, but occasionally obturator nerve stimulation was noted when the areas around the uterine cornu were being treated. The procedures were performed in the lithotomy position using a Karl Storz resectoscope (26F) fitted with a cutting loop. An Eschmann's diathermy TD 411S was used on blend 2 and 150 watts power. A coagulating roller ball was available after April 1990 using 50 watts on blend 1. Glycine (1·5%) was used to irrigate the uterine cavity, and only hydrostatic pressure was used to provide positive pressure by hanging the glycine reservoir one meter above the patient. At no time was a pressure pump used. Negative pressure was obtained from a suction unit and the pressure was varied to achieve sufficient flow of glycine to obtain a clear view. The cervix was always dilated to Hegar 10 to allow both free movement of the resectoscope in the cervical canal and to allow the glycine to flow around the resectoscope should the intrauterine pressure rise, thus diminishing the opportunity for glycine intravasation. At first an attempt was made to monitor the inflow and outflow of fluid, but when it was realised that if the outflow was obstructed for any reason the inflow of glycine ceased, this estimation was abandoned. The patients were not catheterised.

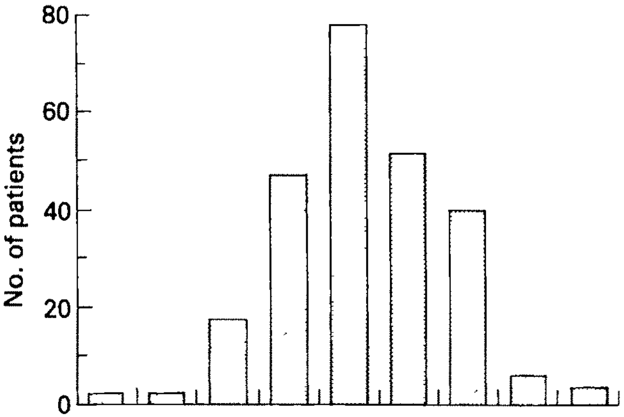

Fig. 1. Age distribution of patients.

Initially the cutting loop used was at right angles to the long axis of the resectoscope but in April 1990, at the same time as the roller ball was introduced, a cutting loop with an obtuse angle was available to improve access to the fundus. A further modification was made to the resectoscope in September 1990. Extra effluent holes were drilled on the distal end of the outer sleeve of the resectoscope so that the whole circumference had holes instead of only the anterior surface. This helped remove the bubbles under the anterior wall of the uterus when the instrument was reversed to resect the anterior uterine wall.

Removal of the endometrial chippings in order to maintain adequate vision is critical to the safety of the procedure. Numerous methods were tried but the introduction of a Hegar 8 flushing curette using normal saline at a pressure of 400 mmHg has proved to be the most satisfactory method and was employed after April 1990.

Because of the lack of pre-treatment it was necessary to resect around the cavity twice with the cutting loop, on the first round removing the endometrium and on the second round removing the basal layer and myometrium. Particular care was taken not to increase the depth in the region of the cornu where the myometrium is thin and in the region of the internal os where there is a large vascular plexus. The procedure was performed in a systematic fashion so that depth orientation is not lost ensuring uniform removal throughout the whole uterus. Direct vision was always employed.

Initially the women were asked to return for follow up a month after the procedure and then again in 3 months. It was soon realised that early complications were very rare so that women were then asked to return at 4 months to assess the effectiveness of the procedure. Loffer had shown that results at 4 months after endometrial ablation mirrored those at 8 years (Loffer 1988).

Results were based on the patients' history. If a patient was satisfied and could lead a normal life, the procedure was recorded as successful. However, if she required further treatment of any sort, the procedure was recorded as unsuccessful.

Results

Of the 400 women, 196 were treated after the introduction of the ball diathermy and obtuse angle cutting loop. Of the total, 70 were treated in an outpatient theatre with intra-cervical block only. Partial resection for a local lesion was carried out in 37 (9%) and the remaining 363 (91%) had total TCRE. No patient showed any clinical symptoms or signs of fluid overload.

Uterine perforation occurred in two women. One perforation was at the fundus (case No. 133) while in the other (case No. 75) the internal os was torn and the tear involved the uterine artery. Both these women had immediate laparotomies to check for intra-abdominal trauma followed by an abdominal hysterectomy. There was excessive intra-operative bleeding requiring tamponade with a Foley catheter in four women. One woman (case No. 50) had a large secondary haemorrhage on day 12 necessitating hysterectomy She had had a profuse primary haemorrhage from the region of the internal os causing abandonment of the procedure and control of the haemorrhage with a vaginal pack. When the uterus was removed, there was no evidence of trauma apart form the resection of the endometrium (Table 1).

Although care was taken to investigate women with irregular bleeding and post menopausal bleeding, four were found to have a carcinoma of the endometrium after a TCRE. The first woman had had a hysteroscopy and suction curettage but the histology result was overlooked prior to her TCRE. The second patient with post menopausal bleeding had malignancy diagnosed in an endometrial polyp resected during TCRE. She had previously had a negative hysteroscopy and curettage. The other two patients did not have pre-operative endometrial sampling. All women underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and no residual carcinoma was found in any operative specimens.

Thirty women out of 400 had to stay in hospital for one night or more after their procedure. This was usually due to delay in recovery from the anaesthetic, and all had had their operations in the afternoon. Overnight stay was also more likely in women who were sterilised at the same time. The mean number of days in hospital for these women was 1·8 days (range 1–6 days). This includes the two patients who required hysterectomies and the four who required tamponade with Foley catheter. One patient was readmitted for observation because of bleeding but no treatment was required.

The other 370 patients were treated as day cases. The 70 patients treated as outpatients all went home within 2 h of completing their procedure.

396 women out of the total have been followed for at least 4 months. Two have been lost to follow up and two have died of disease unrelated to their menstrual disorder or TCRE (one woman with epilepsy and the other status asthmaticus).

At the 4 month follow-up, 336 (85%) were satisfied with their initial TCRE and required no further therapy. The remaining 60 women (15%) were dissatisfied and 24 elected to have hysterectomies (including the four women with carcinoma and two women requiring immediate intra-operative hysterectomies). Of the remaining 36 women, 31 elected to have a further TCRE and five women who were dissatisfied requested no further management. Of those who had a second TCRE, three subsequently have had hysterectomies. The total number of hysterectomies therefore is 27 (6·8%). One patient has had three TCREs and was finally satisfied. After recurrent TCRE for those women who required it, 364 (92%) were satisfied with their treatment. There was no difference in the success rates in women treated under local anaesthesia as outpatients where 5 patients of 70 were dissatisfied (7%).

Table 1. Number and percent of major complications

Uterine perforation	2 (0·46%)
Primary haemorrhage requiring tamponade	4 (0·93%)
Secondary haemorrhage requiring hysterectomy	1 (0·23%)

After the operative techniques were altered (ball diathermy, obtuse angle diathermy loop and flushing curette) 196 had the procedure and 22 (11.2%) in this group were dissatisfied after their initial TCRE. This compares with 38 dissatisfied patients in the first 200 patients treated (19%) (a 2×2 contingency table was constructed against the null hypothesis which shows there is a difference between treatments $P<0{\cdot}05$ and $>0{\cdot}01$).

Partial resections were performed in 37 patients for local lesions and four were dissatisfied (10·8%). One patient subsequently had a myomectomy, one an abdominal hysterectomy and bilateral salpingo-oophorectomy for carcinoma and two required vaginal hysterectomies.

Discussion

The concept of endometrium destruction by various methods is not new (Schenker & Polihuk 1973; Goldrath *et al.* 1981). However, the introduction of the operating hysteroscope has now allowed the endometrium to be destroyed under direct vision and also allows for the treatment of local intra-uterine disease.

Our experience with 400 patients, the majority of whom would have been treated by hysterectomy, shows that 85% of women are satisfied with this form of treatment after one TCRE and 92% are satisfied if the procedure is repeated.

Major complications occurred infrequently and only three patients required urgent hysterectomies (two perforations and one secondary haemorrhage). We have experienced no clinically obvious complication related to fluid overload. We feel that the technique used (dilatation of cervix to Hegar 10 to allow fluid to flow past the resectoscope and not employing a pressure pump) has contributed to this.

Examination of women with ultrasound confirming the presence of myohyperplasia (anterior and posterior wall of the uterus each in excess of 1·5 cm) is an important safety factor as, in both the patients who had perforations, this factor was lacking.

The procedure overall is safe with a low complication rate but adequate training is required. Extensive experience with diagnostic hysteroscopy is essential before operative hysteroscopy is attempted. Direct vision facilitates manipulation of the endoscope and makes it easier to feel the resistance of the uterine wall contributing to the low complication rate. The absence of pre-treatment and operating at any time in the menstrual cycle may increase operating time because of the increased bulk of the chippings (these can be easily removed with the flushing curette) but does not decrease the success of the treatment as compared with other series, and certainly makes the organisation much easier.

It is difficult to ensure amenorrhoea; because of this, patients were not led to expect that this would be the result. Indeed it was apparent with a few patients that they would not be satisfied with anything but complete cessation of menses, and in this situation hysterectomy is a better form of treatment.

It is difficult to compare the results of TCRE with other methods (laser and radio-frequency induced) of endometrial ablation. However electrocautery does have the following positive features:

1. Pre-surgical histopathological assessment is not required because an excellent pathological specimen is obtained.
2. There is no evidence of fluid overload if positive pressure from a pump is not used.
3. It is suitable for day-case treatment or as outpatient treatment with local anaesthesia.
4. Medical pre-treatment is not necessary.
5. Apart from the resectoscope, the equipment is found in normally equipped general operating theatres so that the necessary capital expenditure is small.
6. Surgeons and theatre staff are familiar with the power source used.

In conclusion, TCRE appears to be a great advance in the management of menstrual disorders provided the surgeon is well trained. It offers simple and effective treatment to patients whose menstrual loss is affecting their lives but who feel that hysterectomy is too radical a solution. Some women do not seek treatment because of a fear of the relatively major procedure of hysterectomy. As TCRE becomes established, the number of women seeking treatment may increase. Amenorrhoea should not be the goal—rather, the procedure should be offered to reduce significantly menstrual loss, thus allowing women to lead normal social lives and avoid major surgery. Its major deficiency at this moment is the lack of long term follow-up data. There is also the possibility that carcinoma of the endometrium may present late after TCRE, especially in amenorrhoeic patients, whereas if these women had had hysterectomy, they would no longer be at risk.

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FERTILITY CONTROL

Randomised comparative study in 217 women of three disposable plastic IUCD thread retrievers

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ABSTRACT

Objective To assess the relative efficacy of three disposable plastic instruments in the retrieval of 'missing' IUCD threads.

Design A prospective randomised comparative single centre study.

Setting Family Planning Clinic in London, UK.

Subjects 217 of 350 IUCD users referred to the research team with 'missing' IUCD threads entered the study.

Intervention All women initially underwent exploration of the endocervical canal with Spencer Wells forceps. When this procedure did not retrieve the threads, the patients were entered into the study. A maximum of two randomly chosen plastic IUCD thread retrievers were then used in any one patient to explore the uterine cavity and capture the 'missing' threads. The order in which the two retrievers were employed was also determined at random. Four separate entries into the uterine cavity were permitted with each instrument, the endocervical canal being explored with Spencer Wells forceps after each retraction of the instrument to identify the possible descent of the threads.

Main outcome measures Threads brought down beyond the external cervical os, or threads brought to within the endocervical canal and then grasped by Spencer Wells forceps.

Results In approximately 40% of all patients, the threads were retrieved with Spencer Wells forceps alone and a further 40% with the disposable plastic retrievers. About 5% had no retrievable threads, and only 2·5% of the referred patients required general anaesthesia for removal of their IUCD. The analysis of the comparative trial was confined to the 197 patients with retrievable threads which could not be brought below the external os with Spencer Wells forceps. The first plastic retriever used was successful in 50% of patients. The Retrievette (59%) and the Emmett (53%) performed better than the Mi-Mark Helix (37%) in this study. The difference was statistically significant (P=0·03) and the 95% confidence interval for the difference of the Mi-Mark Helix from the other two retrievers was 4% to 33%. This retrieval rate for the Mi-Mark Helix was much worse than in previously reported studies, though one doctor did have a better success rate with this retriever. The success rates, using a second plastic retriever randomly chosen from the two not used in the first attempt, were almost identical to those observed with the first retrievers: 63%, 56% and 36%. The success rate did not appear to be influenced by the length of thread, day of cycle, device type or parity. The success of the second retriever tried did not seem to be influenced by the retriever that had failed previously.

Conclusions Based on our experience, the initial exploration of the endocervical canal with Spencer Wells forceps is invaluable. If this simple manoeuvre fails to retrieve the 'missing' threads, either the Retrievette or the Emmett thread retrievers are useful tools in general practice or in the family planning clinic setting.

The vast majority of intrauterine contraceptive devices (IUCDs) used worldwide have a tail that enables the user or physician/nurse to verify the presence of the IUCD and to facilitate removal of the device. Concern arises when, on physical examination, the thread cannot be felt or seen since this may signify unnoticed external expulsion or displacement of the device within the uterine cavity, or more seriously, partial or complete translocation. An enlarging pregnant or fibroid uterus is another reason for thread retraction.

There is little firm information on how frequently IUCD threads go 'missing', but a survey in 1983/84 based on 16

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clinics within the UK IUD Research Network which involved questioning 202 IUCD users who attended for follow-up on two randomly chosen days, showed that 7% had 'missing' threads (UK IUD Research Network 1984). In another prospective study of 628 IUCD users, 9% were found to have absent threads at their follow-up visits (Chamberlain 1982).

The clinical management of such women is thus a common problem in general practice and in family planning and gynaecology clinics. It frequently causes much anxiety for the woman concerned. Diagnostic ultrasound is often used to exclude pregnancy and locate the IUCD. A common clinical practice is to admit the woman to hospital for removal of the device under general anaesthesia. Many authorities consider this over-treatment.

Over the past two decades, various schemes for outpatient retrieval of 'missing' IUCD threads have been proposed (Valle *et al.* 1977; Guillebaud 1980; Prendiville & Stirrat 1984; Johnson & Moodley 1988), including the use of disposable plastic IUCD thread retrievers (Husemeyer & Gordon 1979; Guillebaud 1980; Pap de Pesteny *et al.* 1986). Three such retrievers are available in the UK. They are the 'Mi-Mark Helix', the 'Emmett IUCD Thread Retriever' and the 'Retrievette IUCD Thread Retriever'. All are designed for easy use in family planning clinics and physicians' offices with avoidance of general anaesthesia and yet minimal discomfort. However, widely differing success rates have been demonstrated using the same instrument (Husemeyer & Gordon 1979; Bromham & Bowie 1980; Chamberlain 1982) and comparing different instruments, mainly in uncontrolled studies. The purpose of the present randomized study was to determine the relative success rate of the above three instruments when used in a family planning clinic setting, following a common protocol.

Materials and Methods

Description of retrievers (see Fig. 1)

The three devices were used according to their manufacturers' instructions:

The 'Mi-Mark Helix' consists of a flexible, loosely wound, flat helix of soft inert plastic on a firm plastic stem, which was originally designed for obtaining endometrial mucus for cytological examination. The helix is introduced through the cervical canal with clockwise rotation. Once inside the uterus, clockwise rotation is continued in order to entwine the threads, and the device is then withdrawn whilst maintaining rotation. If no threads are seen at the external os, the cervical canal should be explored with Spencer Wells forceps. The procedure may be repeated (up to a total of four times in this study) if the first attempt fails to bring down the threads (Husemeyer & Gordon 1979, Manufacturers' instructions for the use of the Mi-Mark Helix).

The 'Emmett IUD Thread Retriever' is a soft, flexible, straight plastic rod on a firm plastic stem. The lateral sides of the plastic rod contain numerous notches, designed to entrap the IUCD threads. The retriever is inserted into the uterus, and the posterior, anterior, and both lateral walls of the cavity are swept in turn by the notched edges of the retriever while it is gradually withdrawn from the uterus (Manufacturers' instructions for use of the Emmett IUD Thread Retriever).

The 'Retrievette IUCD Thread Retriever' consists of a relatively firm handle and a flexible curved distal rod with a rounded cross section. The concave surface of the rod contains three notches, designed to catch the threads of the IUCD. After cleansing the cervix, the retriever is inserted through the cervical canal up to the fundus, twisted through 180 degrees and retracted slowly with slight pressure of the concave surface towards the uterine wall. If the first retraction is unsuccessful, the procedure is repeated three more times with the concave side of the instrument directed to the remaining walls (Manufacturers' instructions for the use of the Retrievette).

The maximum number of explorations of the uterine cavity with each device was limited to the four described above and, unless the threads were brought down beyond the external cervical os, each procedure with any device was followed by exploration of the endocervical canal with Spencer Wells forceps. In order to avoid undue discomfort for the woman, it was decided to use only two of the three retrievers in any one woman. The choice of the two retrievers and the sequence in which they were to be employed was made by random allocation. All the women were seen by a selected small group of family planning doctors highly experienced in IUCD fitting.

Clinic Protocol

Women with lost IUCD threads were referred to the MPC

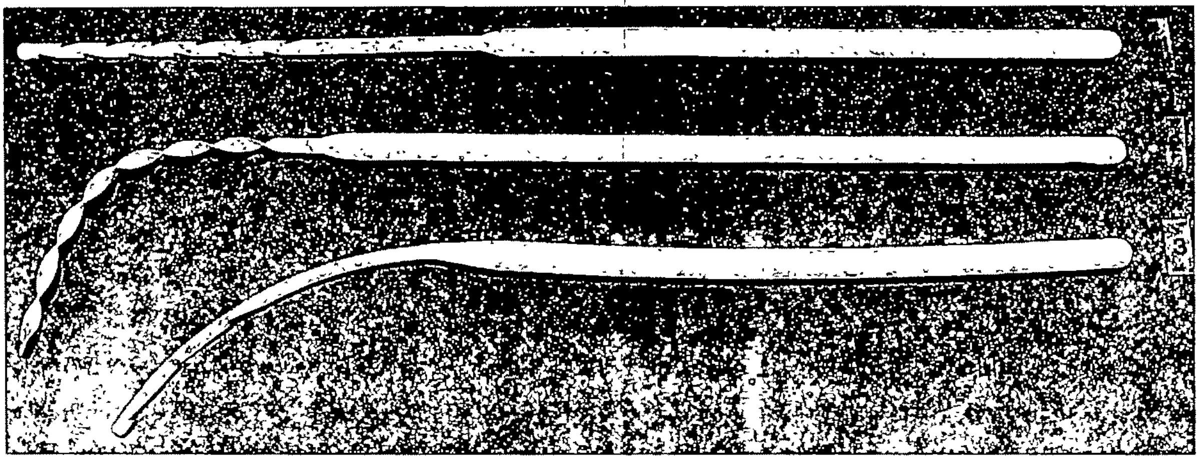

Fig. 1. (1) Emmett IUD Thread Retriever; (2) Mi-Mark Helix; (3) Retrievette IUD Thread Retriever.

Table 1. Comparability of the women by the first plastic retriever in the comparative trial. Values refer to number of women, not per cent Figures in brackets denote number of women for whom the relevant variable was not recorded

	Mi-Mark Helix	Emmett	Retrievette
Number of women	67	62	68
Threads > 5cm	39 (4)	35 (2)	37 (3)
Day of cycle > 14	21 (2)	21 (2)	16
Nulliparous	38	35	40 (1)
Gravigard (=73% of devices)	51	43 (2)	49

research team by medical colleagues from within the MPC general clinic, by other family planning clinics and by general practitioners. To minimize the risk of exploring an already pregnant uterus, the clinic visit was scheduled during the first ten days of the menstrual cycle. Even if this was not feasible, pregnancy was excluded in all cases. Detailed obstetric, gynaecological and contraceptive histories were recorded. The women were told that there were three plastic devices available, which we believed would be successful in retrieving missing IUCD threads, but that we needed to find out whether one was better than the other. They were asked to allow us to use the instruments in a scientific comparative way and their verbal consent was obtained. They were also informed that, if the plastic retrievers failed to retrieve the threads, we would, with their permission, use instruments designed to retrieve the entire IUCD, as is routine clinic practice. They were offered the option of local anaesthetic. A pelvic examination was performed.

After cleansing the cervix, the endocervical canal up to the level of the internal os was explored with Spencer Wells forceps, opening and closing the instrument within the canal. This is a routine clinic procedure. In some cases the threads were seen before being grasped; in other cases retrieval was 'blind'. Only those women in whom this procedure did not succeed in bringing down the threads were recruited for the study. A uterine sound was then passed to determine the presence of the IUCD *in utero*. Where necessary, an Allis forceps was applied to steady the cervix and straighten the canal. The randomly chosen first retriever was then used in the manner described above. If it failed, the second instrument (randomly chosen from the two not so far used) was then employed. If neither instrument was successful, one or more of a variety of IUCD retrievers (Grafenberg hook; Birnberg hook; Patterson Alligator forceps) were used in an attempt to retrieve the IUCD itself.

The criteria for success were either threads brought down beyond the external cervical os or threads brought to within the endocervical canal and then grasped by Spencer Wells forceps.

Table 2. Success rate by number of retrievers used, excluding unsuitable women.

Retrieval instrument	Cases	Success	Rate	95% CI*
First instrument	197	98	50%	(43%–57%)
Second instrument	99	52	53%	(43%–62%)

*CI = confidence interval

Statistical methods

Treatments were allocated sequentially from a list of pairs of different retrievers prepared by simple randomisation. Confidence intervals for the difference in proportions are given based on the normal approximation. The significance levels for the difference of the Mi-Mark Helix from the Retrievette and Emmett were computed by 2000 random simulations of the differences that would have been observed in a similar trial in which there was no difference in success rate between the methods. These significance levels allow for bias due to concentrating attention on the retriever with the smallest success rate, and corresponded closely to the overall contingency tables χ squared of the difference between retrievers. The relation between success and other factors was investigated using logistic regression, and the details are not presented here.

Owing to possible concern over bias in the results from the second plastic retriever, all probability calculations have been based on the first plastic retriever only. However, the results of the second retriever appear almost identical to the first plastic retriever used and if they were regarded as independent then significance levels would be considerably smaller, and confidence intervals narrower.

The target sample size of 200 women was a compromise between the amount of time it would take to complete the study and the size of the confidence intervals that would be produced. There was an interim analysis at approximately half way through this trial; no allowance has been made for this interim analysis as the decision whether to continue was too complex to model. The analysis was done using Minitab 5·1 at the University College London central computer service.

Results

Approximately 350 women were referred during the study.

Table 3. Success rates by type and sequence of instruments used, excluding unsuitable women

	Cases	Success	Rate	95% CI*
First instrument				
Mi-Mark Helix	67	25	37%	(26%–49%)
Emmett	62	33	53%	(41%–66%)
Retrievette	68	40	59%	(47%–71%)
Second instrument (see text)				
Mi-Mark Helix	28	10	36%	—
Emmett	36	20	56%	—
Retrievette	35	22	63%	—

*CI = confidence interval.

Differences between instruments, first attempt only. χ^2=6·68, df=2, P=0·04

Confidence intervals of difference, first attempt only. Emmett and Retrievette versus Mi-Mark Helix: 4%–33%, Retrievette versus Emmett: –11%–23%.

Table 4. Success rate by doctor and instrument. First instrument only (Number of women with each instrument in brackets).

Doctor	Mi-Mark Helix	Emmett	Retrievette
A	40% (45)	52% (44)	63% (46)
B	11% (9)	38% (13)	45% (11)
C	60% (10)	100% (3)	43% (7)
The rest	0% (3)	100% (2)	75% (4)

Initial use of the Spencer Wells forceps in the cervical canal was so successful in retrieving the threads that only 217 remained for admission to the study. Of these, 20 were excluded from the comparative analysis for the following reasons. First, subsequent evidence indicated that the IUCD did not have any threads at all (17 women, 2 of whom required general anaesthesia). Secondly, the IUCD was embedded in deformed uterine cavity due to fibroids (1 woman); subsequent attempts to retrieve the IUCD failed and this woman had a hysterectomy three years later. Thirdly, there was vaso vagal reaction during outpatient sounding of the uterus, hence no opportunity to try any retriever; general anaesthesia was given later (1 woman). Finally, subsequent evidence was that there was no IUCD in uterus (1 woman); (subsequent laparoscopic retrieval of a Copper-7 device that had perforated the uterus).

The following report relates to 197 women (90% of those recruited to the comparative study). Of these, 143 (73%) used the Gravigard; 19 (10%) the Mini-Gravigard; 21 (10%) other copper-bearing devices (Multiload, Mini-Multiload, Novagard, Ortho-Gyne-T); and 12 (6%) the Lippes Loop, while in the remaining 2 (1%) the type of device was not recorded.

Table 1 shows the result of the random allocation on the distribution of parity, day of cycle and thread length between retrievers. The overall success rate, using only one plastic retriever, was 50% (Table 2), whereas using a second, different instrument after the failure of the first, increased the success rate to 76%. Table 3 shows the success of each of the three retrievers when first and second attempts were analysed separately. As can readily be seen, the Emmett and the Retrievette retrievers gave consistently better results (53% and 59%, respectively, at the first attempt) compared to the Mi-Mark Helix (37%). This difference is statistically significant. Likewise, similar success rates for each of the three retrievers were achieved when they were used as the second instrument after failure with the type allocated initially. The overall success rate (Table 2) of the three instruments used in the second attempt (53%) was similar to that of the three retrievers used in the first attempt (50%).

The doctors varied in their overall success rate and in the response for each instrument, as demonstrated in Table 4. Considering all doctors as one group, there was a statistically significant difference between the three instruments, but when analysing the data separately for each operator, only the results for doctor A came close to statistical significance (χ^2=4·84, P=0·10). This is not surprising, given the relatively small number of patients seen by the remaining doctors.

Other variables (parity, length of thread and device type) did not appear to affect the success rate of the three retrievers. The Retrievette appeared to perform less well in the second half of the cycle but the numbers are too small to allow firm conclusions.

All women in whom neither instrument was successful were followed up to determine the eventual method of retrieval of the devices (all of which still bore threads). There were 47 such cases, including four in whom the device was removed under general anaesthesia. Details are listed in Table 5.

Pain relief

The trial protocol did not incorporate objective measurement of pain relief, but the investigators' clinical impression was that the majority of women found the retrieval procedures acceptable without the need for analgesia or local anaesthesia. However, it is the policy of 'Dr A' (who saw 69% of all patients) routinely to offer local anaesthesia: 10–15 ml of plain lignocaine 1% used paracervically at 3–4 and 8–9 o'clock positions injected at a depth of 2 cm prior to any intrauterine manipulation. This affords effective pain relief, but is unnecessary for exploring the cervical canal with Spencer Wells forceps, normally a pain-free manoeuvre.

Approximately 30% of women seen by 'Dr A' accepted the offer of local anaesthesia. In his opinion, the plastic retrievers cause less cervical or fundal pain (irrespective of the use of local anaesthesia) than metal hooks.

Discussion

One of the most useful findings from this, the largest reported series of cases, was that in about 40% of all women referred, the threads were readily retrieved from within the cervical canal by means of Spencer Wells forceps. This easy and relatively painless procedure should thus be considered as the first routine step in the management of patients with missing IUCD tails. It is also relevant to interpretation of the (subsequent) success rates of the three retrievers in our study. Other things being equal, any study without this preliminary manoeuvre would be bound to show a higher success rate with any retriever design.

Attempting retrieval with only one of the three instruments under study was successful in 50% of the remaining cases with retrievable threads, but the success rate rose considerably to 76% when a second instrument was added.

Table 5. Eventual method of thread/IUCD retrieval in unsuccessful cases (n = 47).

Method	Numbers
Metal hook (mainly Birnberg design)	33
Patterson (Alligator) forceps	3
Spencer Wells forceps (approx 2 years later)	1
Novak curette	4
IUCD expelled with next menses	1
Repeated numerous attempts with Spencer Wells forceps	1
General anaesthesia	4
(Hook)	(1)
(Polyp forceps)	(1)
(Spencer Wells)	(1)
(Instrument not recorded)	(1)

Looking at the three specific retrievers under investigation, we found the success rates for the Retrievette and the Emmett retrievers to be very similar, but the Mi-Mark Helix did less well, irrespective of whether it was used as the first, or as the second instrument.

Our success rate of 53% for first use of the Emmett retriever is comparable to the 57% reported by the UK IUD Research Network in 1984, and better than the 40% observed in a more recent study (Johnson *et al.* 1990).

In our series the Retrievette was more successful than in an earlier UK study where it succeeded in 48% of cases (UK IUD Research Network 1983), but it performed less well than in a Swedish trial in which the success rate was 80% (Pap de Pesteny *et al.* 1986). These results have not been replicated elsewhere and may in part be due to intensive practice and experience.

Our findings for the Mi-Mark Helix are somewhat disappointing compared to the excellent results of 84% and 71% obtained by Husemeyer & Gordon (1980) and Ansari & Hoffman (1982), respectively, but better than the poor performance of the Helix of 7·7% observed by Bromham & Bowie (1980). Yet interestingly, one of the doctors in the present study had better success (60% in 10 attempts) with this retriever compared to the other operators, which may reflect a personal preference or dexterity in its use.

Of the 47 women in whom the plastic retrievers failed, 33 (70%) had the threads/IUCDs retrieved with a metal hook, with the Birnberg hook the preferred choice. It is narrower than the Grafenberg hook, can be manipulated more easily than the latter, and is stiffer than the Retrievette which made it easier to locate the IUCD, particularly by feeling the corrugations of the copper wiring on the stem of the device, or the plastic twists of non-copper devices such as the Lippes Loop or Saf-T-Coil. A drawback of the Emmett design is that its bulbous end makes it more difficult to feel the device.

Other authorities favour the use of various retrieval forceps (Johnson *et al.* 1990; Onwude *et al.* 1991) with or without thè hysteroscope (Valle et al. 1977) to see the IUCD. This approach does not require the persistence of a thread or threads on the device. However, for outpatient or GP surgery retrieval, disposable plastic retrievers are more practical, and this study supports the use of either the Retrievette or the Emmett design. We would also reemphasize the value of first trying with narrow Spencer Wells type forceps to identify/retrieve threads that are not above the level of the internal cervical os. If both these fail, referral to a dedicated clinic will be appropriate. Usually after ultrasound scanning (with a back-up X-ray should no device be found in the uterus) and ideally appropriate pretreatment of the cervix, most remaining IUCDs will be removable with the 'Rocket IUD Retrieving Forceps' (Johnson *et al.* 1990) or equivalent. Cervical pretreatment has been shown to be beneficial: with ethinyloestradiol 50 μm twice a day orally for five days (Prendiville & Stirrat 1984); Lamicel transcervical dilators (Johnson & Moodley 1988); or with the progesterone antagonist RU 486 (Mifepristone) (Gupta & Johnson 1990). Premedication with mefenamic acid 500 mg (Ponstan) is valuable, but practitioners should have a low threshold for use of local anaesthesia (Guillebaud & Kasonde 1979).

It is significant that only nine (2·5%) of the women referred or 4% of those in whom the plastic retrievers were tried, needed general anaesthesia. This suggests that specialized 'IUCD problem' clinics equipped with retrieval instruments of different designs, and to which women could be referred from a variety of sources, would be a cost-effective and less invasive method of dealing with 'missing' IUCD threads.

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CASE REPORTS

Recurrent miscarriage, cystic hygroma and incontinentia pigmenti

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Case report

In her first pregnancy in 1981, the propositus, II.2 (see pedigree, Fig. 1), then aged 22 years, presented at 26 weeks from her last menstrual period with no fetal movements. An ultrasound scan showed a single fetus with no heart pulsation and a biparietal diameter equivalent to 16 weeks. The pregnancy was terminated and at post-mortem the fetus, although macerated, was seen to have a large nuchal cystic hygroma. The karyotype from the chorion was 46, XY. The following year she was delivered of an apparently healthy female infant at term, III.2, who developed a right-sided hemiparesis following an illness, described as 'meningitis', at 5 weeks of age. However, no pleiocytosis of the cerebrospinal fluid was detected and all cultures were sterile. In her third pregnancy in 1991 to a new partner, a booking scan at 16 weeks revealed cystic hygroma and generalized oedema in a single fetus with a biparietal diameter measurement equivalent to 14 weeks. A chorion biopsy undertaken to exclude chromosomal abnormality showed 46, XY. When she reattended the clinic a week later, the fetal heart pulsations were absent on ultrasound and the pregnancy was terminated by suction evacuation. Following this the propositus was referred for genetic counselling. Review of her general medical records disclosed a letter in 1972 in which a dermatologist, who had seen her because of atopic dermatitis, had noted classic pigmentary changes of incontinentia pigmenti.

Examination of the propositus revealed the typical changes of incontinentia pigmenti with whorled pigmented lesions in the left axilla and on the chest wall (Fig. 2), as well as fine depigmented streaks on her arms and legs. She also had a central vitreous opacity of her right eye which was smaller than her left. Her daughter, III.2, had typical pigmented streaks of incontinentia pigmenti and a slightly short right leg with a mild right hemiplegia. The mother of the propositus, I.2, and her two sisters, II.6 and II.7, were also found to have clear evidence of incontinentia pigmenti on examination. II.6 gave a history of two first trimester miscarriages, while II.7 also had experienced two miscarriages, one at 12 weeks gestation, the other at 19 weeks by dates but of 12 weeks size. Karyotyping on these miscarried fetuses was not done and their sex is not known.

Discussion

Recurrent miscarriage and fetal cystic hygroma are both indications for determining the karyotype of both the parents and the fetus. Karyotype abnormalities are said to occur in 60–80% of fetuses with cystic hygroma (Edwards & Graham 1990), the most common being 45, X (Turner's syndrome), followed by autosomal trisomies.

Incontinentia pigmenti (Bloch–Sulzberger syndrome) is an X-linked dominant disorder characterized by the development of cutaneous linear vesiculation in early infancy and neurological involvement (mental retardation, spasticity, microcephaly, hydrocephalus, ocular abnormalities) in a quarter of cases (Baraitser 1990). The skin lesions become

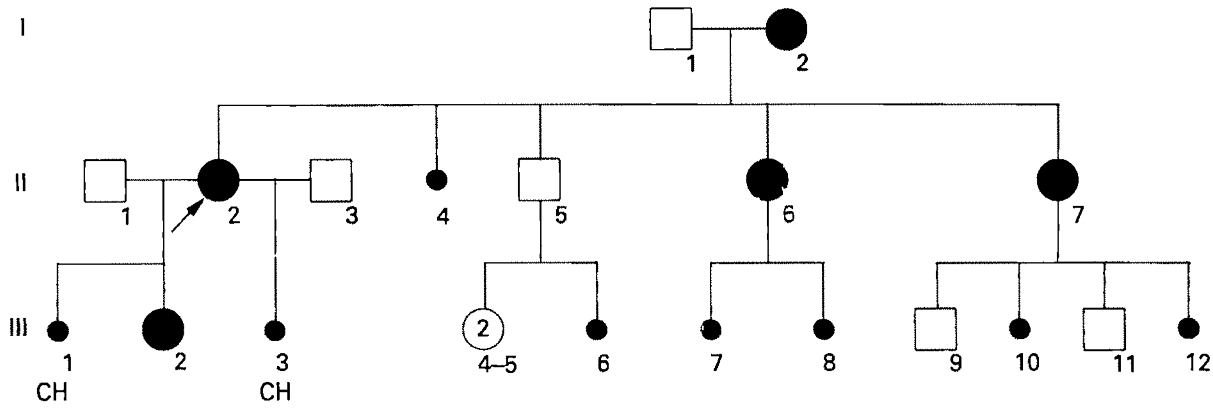

Fig. 1. The pedigree with the propositus, II.2, arrowed. ●; female with incontinentia pigmenti, □, normal male; ●, miscarriage; CH, cystic hygroma.

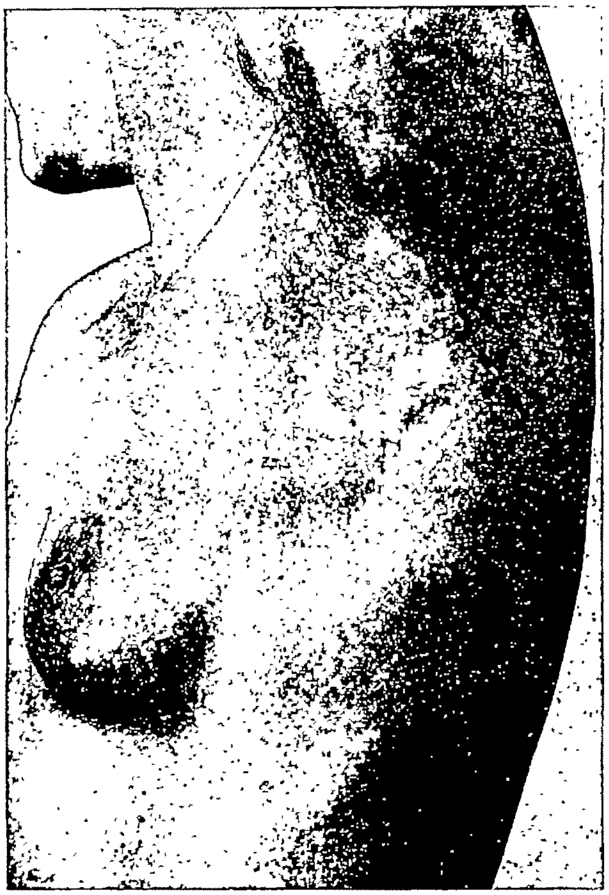

Fig. 2. The left axilla and chest wall of the propositus, showing the typical whorled, pigmented skin lesions of incontinentia pigmenti.

pigmentary by the age of two years but later resolve spontaneously leaving atrophy or depigmentation. X-linked dominant inheritance is suggested by the finding that 97% of those affected are females. Males have only one X chromosome and it is assumed that early fetal loss almost invariably occurs in males who inherit the gene (Carney 1976). Consequently, miscarriage can be expected in one in four pregnancies in carrier women and half of their daughters will be affected. Some isolated cases of incontinentia pigmenti have been associated with an X-autosome translocation involving a breakpoint at Xp11.2 (Cannizaro & Hecht 1987) but molecular analysis in familial cases has shown linkage to Xq28 in one study (Sefiani *et al.* 1989), and no linkage to either locus in another (Hydén-Granskog *et al.* 1991).

Cystic hygroma is a rare developmental anomaly of the lymphatic system characterized by the formation of a multilocular cystic mass of variable size, usually occurring in the region of the head and neck. This has given rise to the alternative terminology· 'jugular-lymphatic obstruction sequence'. A causal relation with aneuploidy is frequent but unexplained. Nonchromosomal causes include Noonan Syndrome and a number of rare autosomal recessive syndromes (Edwards & Graham 1990). We believe this is the first report of cystic hygroma occurring in association with a nonchromosomal X-linked disease, namely incontinentia pigmenti. In this family cystic hygroma occurred in two male fetuses whose deaths can reasonably be attributed to the incontinentia pigmenti gene. Whether affected females develop transient cystic hygroma *in utero* is undetermined.

It is usually stated that incontinentia pigmenti is lethal in early pregnancy for affected males but this is not necessarily so. This family highlights the following important points: (a) the finding of cystic hygroma on prenatal ultrasound is an indication for thorough clinical examination of the mother, with review of her medical notes, prior to an invasive procedure to determine fetal karyotype; (b) thorough clinical examination and review of medical records is indicated for couples presenting with recurrent miscarriage; and (c) a multi-disciplinary approach involving the clinical genetics service has the potential for avoiding unnecessary gynaecological investigations.

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Lacking anastomoses between left and right uterine arteries in uterus bicornis during pregnancy as demonstrated by Doppler velocimetry

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Case report

An 18-year-old nulliparous woman was admitted at 32 weeks' gestation because of pregnancy induced hypertension and fetal growth retardation. Her blood pressure had increased during pregnancy from 120/70 mm/Hg to 150/100 mmHg. Proteinuria was not present. During admission, repeated fetal cardiotocograms showed a normal pattern. Ultrasound examination revealed fetal growth retardation without fetal anomalies. Also, a partial septum was noticed at the midline of the uterine fundus with the placenta localised on the left side of this septum.

As part of a research programme, flow velocity waveforms (FVWs) of the umbilical artery, the fetal internal carotid artery, the fetal renal artery, the fetal aorta and the uterine arteries were recorded using an Acuson 128 pulsed Doppler system. All the pulsatility index (PI) values of the fetal arteries were within our normal ranges. However, the PIs of the left and right uterine arteries showed a remarkable difference with values of 0·80 and 4·27, respectively (Fig. 1). The FVW of the right uterine artery showed a pronounced notch which was not found in the FVW of the left side.

At 34 weeks' gestation, the woman became severely pre-eclamptic and was delivered by elective caesarean section of a girl weighing 1450 g (below the 10th centile). APGAR scores were 7 (1 min) and 9 (3 min), and the umbilical arterial and venous pH were 7·25 and 7·29, respectively. The newborn required admission to the neonatal intensive care unit. The placenta weighed 285 g and histopathological examination revealed a placenta with varying maturation and two small infarcts. During the caesarean section, the woman appeared to have a uterus bicornis with the placenta completely in the left uterine horn.

Discussion

The incidence of congenital anomalies of the Müllerian system is 1–2% (Dunselman 1959; Ashton *et al.* 1988). The most common anomalies are uterine malformations, which are the result of nonfusion, deficient development or defective canalization of the Mullerian ducts (Golan *et al.* 1989). These anomalies are associated with an increased complication rate in pregnancy, in particular, abortion and preterm labour (Buttram 1983; Ludmir *et al.* 1990), but are also associated with placental abruption and fetal growth retardation (Patton & Novy 1988, Cohen & Chibber 1986).

The difference in PI between the left and right uterine artery in our patient was compared with that of 34 patients with fetal growth retardation (birthweight <10th centile). The mean difference in that group was 0·32 (SD 0·30; range 0·02–1·18), whereas the difference in the presented case was 3·47. Figure 1 demonstrates the extreme difference in left and right PI values in our patient. Obviously this finding is the result of the abnormal FVW with a pronounced notch in the uterine artery of the right horn in which the placenta was not located. The FVW on this side was almost identical to FVWs in uterine arteries of non-pregnant women.

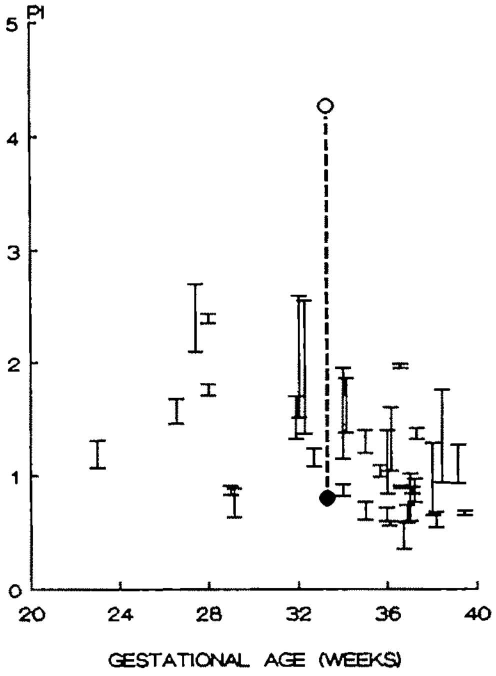

Fig. 1. PI values of left and right uterine arteries of index patient (● = left, ○ = right) and of 34 patients with fetal growth retardation.

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According to Gosling & King (1975), the PI of the uterine artery is a measure of resistance to blood flow downstream; therefore our findings indicate a huge difference in resistance to blood flow between the pregnant and non-pregnant uterine horn. In a normally shaped uterus, vascularisation arises laterally on both sides and assembles an extensive network at the midline by creating anastomoses. It has been suggested that this network of anastomoses is less developed in two incompletely fused uterine horns (Dunselman 1959). In a previous study, we have shown that in normal pregnancies up to 20 weeks, a significant difference was found between the uterine artery PIs of the placental and non-placental side. Afterwards such a difference could no longer be demonstrated (Oosterhof & Aarnoudse 1992). In pregnancies complicated by pre-eclampsia and fetal growth retardation, a slightly increased difference between the left and right uterine artery FVW has been reported (Schulman *et al.* 1987). However, that difference is much smaller than we found in the present case. Bewley (1989) has shown the effect of non-linearity of indices on calculating the magnitude of divergent resistance to blood flow between the left and right uterine artery. If a FVW is recorded with a high ratio, small changes in FVW shape will produce great differences in the calculated ratio. Thompson (1988) has shown that this non-linear effect is stronger if S/D ratios are used instead of PIs. The extreme difference in PIs found in the present case cannot be explained by the non-linearity of the PI.

Our observations indicate the presence of two separate arterial networks in the uterus bicornis, which is most likely the result of lacking anastomoses This could be responsible for the development of pre-eclampsia and/or fetal growth retardation due to inadequate uteroplacental blood flow.

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Polycythemia associated with leiomyoma of the uterus

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Case report

A 53-year-old woman with no children was referred to the haematology department with polycythemia. She had presented initially to her general practitioner with a flu-like illness and a 20 kilogram weight loss over a period of six months On specific enquiry, she had noticed some abdominal distension. She was 3 years post-menopausal and had had no menstrual problems in the past. She had no changes in her appetite or bowel habits and she had never been sexually active.

Physical examination showed obvious plethora but no clubbing or cyanosis. The cardiovascular and respiratory systems were examined and found to be normal. She had a large midline mass arising out of the pelvis and up to the level of the costal margin. This was smooth, firm and non-tender with no associated ascites. The uterus was not felt separately. The haemoglobin concentration was 18·1 g/dl with a haematocrit of 0·58. The red cell indices and white cell count were normal. An abdominal and pelvic ultrasound scan showed a large uterine mass extending from the pelvis to the xiphis-

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ternum which had smooth margins. Other abdominal and pelvic organs appeared normal. Special investigations included arterial blood gases, neutrophil alkaline phosphatase, liver function tests, chest x-ray and electrocardiogram; all were normal.

A provisional diagnosis of a large fibroid uterus was made and this was presumed to be the cause of the polycythemia and a laparotomy was planned. Venesection of 500 ml was undertaken twice to reduce blood viscosity. Her preoperative haemoglobin was 16·1 g/dl with a haematocrit of 0·48.

A total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. The specimen weighed 5·5 kg and consisted mostly of a single fibroid arising from the posterior wall of a normal sized uterus. The blood loss during the operation was 500 ml. She was given low molecular weight heparin 2500 units daily postoperatively and this was continued for five days. Her postoperative course was uneventful except for a low grade fever which resolved spontaneously and for which no cause was found. The haemoglobin on the third postoperative day was 12·9 g/dl with a haematocrit of 0·40. Histologically the tumour was a benign leiomyoma with hyalinised stroma.

She was discharged from hospital on the eighth postoperative day. She was well with no symptoms when reviewed six weeks after the operation. Her haemoglobin, checked at four and six weeks postoperatively, was 13·1 g/dl and 12·8 g/dl (haematocrits 0·37 and 0·36) respectively.

Erythropoietin levels were measured two weeks pre- and four weeks postoperatively using an erythropoietin enzyme immunoassay (Clinigen, Amgen Diagnostics, California, USA). This test involves a monoclonal antibody and polyclonal antibody conjugate in a sandwich enzyme immunoassay. The normal range in our laboratory is <19 mU/ml. The results obtained for our patient of 3·3 mU/ml and 4·4 mU/ml were well within this normal range and showed no significant change.

Discussion

Polycythemia has been observed to occur infrequently in association with uterine fibromyomas. About 30 such cases have been reported since the first description of this association by Thomson & Marson (1953). Removal of the tumour in all cases, so far reported, has been followed by remission although, in many of the reports, the period of follow-up has been short. The mechanism of polycythemia is still not clear, although it has been proposed that the tumour produces erythropoietin autonomously and is not subjected to feedback control mechanisms. Amongst the cases reported so far, only a few demonstrated significant increases in erythropoietin in plasma or tumour extract. In our patient, the erythrocytosis resolved after removal of the uterus, but plasma erythropoietin levels were normal and did not change.

The cases of polycythemia and uterine fibromyomata that have been reported since Thomson & Marson's (1953) first description suggest that this effect is a true entity. In most of these cases, as with other tumours associated with erythrocytosis, the removal of the tumour cured the erythrocytosis (Aboulafia *et al.* 1962; Donati *et al.* 1963; Hertko 1963; Krantz & Jacobson 1970; Naets *et al.* 1977; Payne *et al.* 1969; Thomson & Marson 1953; Weiss *et al.* 1975). Several mechanisms have been proposed to explain the polycythemia. Howitz & McKelway (1955) suggested that the vascularity of the fibromyoma may result in an arteriovenous shunt mechanism and the production of polycythemia. This theory is not supported by the lack of difference between the microscopic appearance of the fibromyomas associated with polycythemia and other fibromyomas. Paranjothy & Vaish (1967) suggested that a very large abdominal mass could interfere with pulmonary ventilation. However, the volume of these tumours associated with polycythemia is not always great enough to disturb the ventilatory mechanism, and measurements of oxygen saturation, whenever performed, have always proved to be normal.

As the kidney is the main organ producing erythropoietin (Krantz & Jacobson 1970), it was suggested that polycythemia, associated with huge abdominal masses, could be due to hydronephrosis or to blood flow changes in the kidney (Babuna *et al.* 1959; Gordon *et al.* 1970). Increased levels of erythropoietin have been observed in some cases of human hydronephrosis and after experimental high ureteral occlusion in the dog (Berger & Sinkoff 1957; Gordon *et al.* 1970). However, hydronephrosis is not a constant finding with polycythemia and, consequently, could not provide a valid explanation in each case. The pathogenesis of the polycythemia may sometimes be explained by the tumour itself secreting erythropoietin. The production of erythropoietin has been demonstrated by other tumours, such as hypernephroma, Wilms tumour, cerebellar haemangioblastoma and hepatoma (Berger & Sinkoff 1957; Donati *et al.* 1963; Eldor *et al.* 1976).

Hertko (1963) and several other authors have shown marked erythropoietin activity in uterine fibromyomas, whereas others failed to demonstrate such activity (Fried *et al.* 1968; Ossias *et al.* 1973, Payne *et al.* 1969). The fact that erythropoietin was occasionally not measurable in the plasma in several cases could be related to the lack of sensitivity of the assay, insufficient to detect normal levels of erythropoietin, and probably insensitive also to moderate increases of the hormone.

It has been suggested by Fried *et al.* (1968) that the active factor produced by certain tumours could be distinct from erythropoietin. In our patient, the serum erythropoietin levels did not show significant change pre- and postoperatively. However, the haemoglobin and haematocrit levels reverted to normal after removal of the fibromyoma.

The enzyme immunoassay method of detecting erythropoietin levels used in our hospital is reliable. It is possible that other humoral factors could be responsible, rather than erythropoietin alone. Polycythemia has been reported in association with leiomyomas of organs other than the uterus, such as leiomyoma of oesophagus (Fried *et al.* 1968) and cutaneous leiomyoma (Eldor *et al.* 1976). It seems possible that the smooth muscle cell itself can be responsible for the inappropriate secretion of erythropoietin or an erythropoietic factor.

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Aggressive angiomyxoma of the female pelvis and perineum. Report of two cases and review of the literature

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Case Reports

Patient 1

A 15-year-old girl was referred to our institution with the diagnosis of vulvar cyst. On examination a soft, painless mass of the left vulvar region, 3 cm in diameter, was noted. A simple excision was performed. The surgical specimen measured 4 × 2·5 × 3 cm. Grossly the tumour was apparently not encapsulated and the cut surface had a glistening gray-myxoid appearance (Fig. 1). The tumour was composed of loosely textured and myxoid population of mesenchimal cells with a prominent vascular component. The histological diagnosis was aggressive pelvic angiomyxoma. The tumour had infiltrative borders and, subsequently, the patient underwent a wide local excision. No recurrence has been detected during a 12-month follow-up period.

Patient 2

A 49-year-old woman presented with a 10 cm lump in the right ischial region which was thought to be a lipoma. At surgery, a well-defined but not encapsulated ischiorectal tumour extending to the pelvic floor and vagina was found. The mass was excised incompletely. On gross inspection, the pinkish-brown surgical specimen measured 9 × 6 × 5 cm, and the cut surface was described as slippery, translucent and soft. The tumour contained a sparse population of spindle-shaped or stellate mesenchymal cells widely distributed in a loose myxoid background with a prominent vascular pattern (Figs. 2 and 3). At the periphery, the myxoid tissue was seen extending into skeletal muscle, connective tissue or neural elements. A post-operative CT scan showed a right ischioperineal mass extending to the ischiorectal space and vagina. A complete

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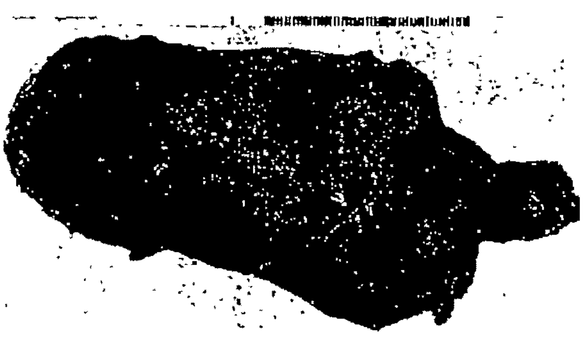

Fig. 1. Case 1. Polypoid tumour with reticulated, gray cut surface.

excision was performed by a combined abdomino-pelvic route; the uterus and its appendages were also removed. There was no evidence of recurrence at the time of the last follow-up, 6 months after the second surgical excision.

Discussion

Aggressive angiomyxoma is a rare but well-described neoplasm with a predilection for the female pelvic soft parts. The lesions are characterized by a predominantly myxoid pattern, different modes of presentation and locally infiltrative behaviour with tendency for multiple recurrences (Steeper & Rosai 1983; Bégin *et al.* 1985, Vaz-Romero *et al.* 1989). We present two additional cases of aggressive angiomyxoma of the female pelvis and review 23 from previously published reports.

A distinct variant of myxoid neoplasms of the female pelvis and perineum was reported by Steeper & Rosai (1983) in 13 women aged 21 to 38 years. They use the term aggressive angiomyxoma to describe a tumour with a characteristic clinical course and particular gross and microscopic features.

Earlier case reports regarded these tumours as varieties of mesenchymal tumours with secondary myxoid changes. Bégin *et al.* (1985) reported nine additional cases of aggressive angiomyxoma in patients aged between 18 and 63 years, two of whom were male. Our first patient is the youngest woman with aggressive angiomyxoma so far described. Vaz-Romero *et al.* (1989) presented the only example of aggressive angiomyxoma of the vagina in a pregnant woman. A review of the clinical characteristics of these cases is shown in Table 1.

The proposed name of aggressive angiomyxoma of the female pelvis and perineum accurately describes its clinical and pathological appearance. Angiomyxoma refers to the microscopic appearance of the tumour which resembles that of a myxoma with a well-developed vascular component. The adjective 'Aggressive' emphasises this important behavioural feature. Examples of this tumour type in any location of the body other than the pelvis and perineum have not been reported.

On gross examination these tumours are characteristically soft, bulky masses, measuring between 3 and 60 cm in greatest dimension. The external surface is smooth and usually appears not to be encapsulated. Some have finger-like projections that extend into neighbouring tissues. The cut surface reveals a glittering, gray tumour of homogeneous consistency with focal areas of congestion and haemorrhage.

Microscopically, the tumours are composed of loosely textured myxoid stroma with populations of small mesenchymal, stellate and spindle-shaped cells. Tumours display a prominent vascular pattern in which dilated blood vessels of varying sizes are distributed haphazardly throughout the myxoid background. The infiltrative nature of these tumours can be appreciated at their periphery where the myxoid tissue is seen extending into skeletal muscle, fat or other structures.

A wide variety of benign and malignant mesenchymal tumours must be considered in the differential diagnosis of aggressive angiomyxoma (Mackenzie 1981; Enzinger & Weiss 1983), such as myxomas (Enzinger 1965), myxoid neurofibromas, vaginal botryoid pseudosarcoma (Chirayil & Tobon 1981), myxoid liposarcoma, myxoid variant of malignant fibrous histiocytoma (Weiss & Enzinger 1977), myxoid leiomyosarcoma and sarcoma botryoides (Chen *et al.* 1980). In contrast to aggressive angiomyxoma, the distinctively prominent vascular component is usually absent in most of these tumours. Myxoid liposarcoma is characterised by a plexiform and arborising pattern of thin-walled vessels and lipoblasts, features which are conspicuously absent in the aggressive angiomyxoma.

This tumour is manifested as a polypoid or cyst-like lesion or as an ill-defined swelling in the pelvic space. The tumour characteristically grows slowly and insidiously, has no capsule, and is locally invasive, extending into neighbouring tis-

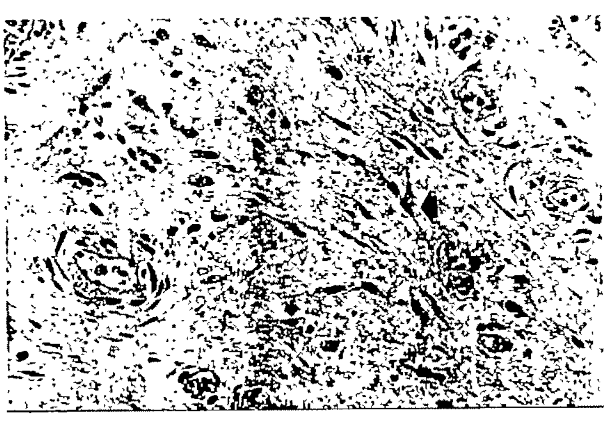

Fig. 2. Elongated or stellate mononuclear cells (arrow) embedded in a myxoid and vascularized stroma (haematoxylin and eosin × 250)

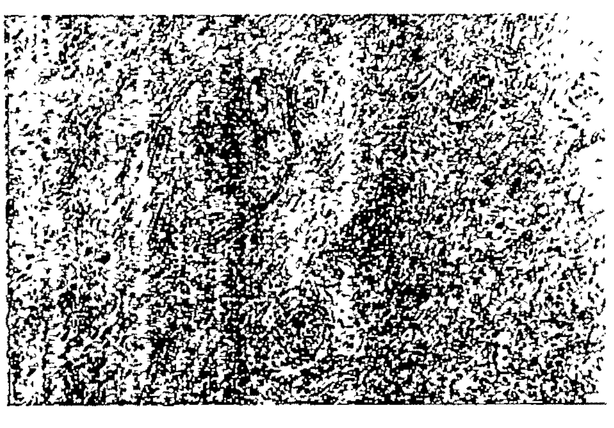

Fig. 3. Vascular spaces of different type, size and shape (haematoxylin and eosin ×100).

Table 1. Aggressive angiomyxoma of pelvis and perineum.

Case	Age/Sex	Location	Size (cm)	Evolution, follow-up
1	21/F	Vulva	14 × 10 × 8	Local recurrence, 2 years
2	33/F	Pelvis & perineum	11 × 6	Two local recurrences, 14 and 15 years
3	25/F	Vulva & ischiorectal fossa	18 × 12	Local recurrence, 3 years
4	26/F	Vulva	14 × 9 × 5	No recurrence, 5 years
5	38/F	Vulva	5 × 5 × 3	Local recurrence, 21 months
6	34/F	Pelvis gluteal region & retroperitoneum	60 × 20	Incompletely excised re-excision 2 months
7	32/F	Vulva & obturator fossa	25 × 6	No recurrence, 4 months
8	28/F	Vulva	3 × 3	No recurrence, 6 months
9	31/F	Pelvis & perineum	10 × 7 × 3	No recurrence, 9 months
10	37/F	Pelvis	Unknown	Three local recurrences: 2, 5 and 7 years
11	23/F	Vagina	Unknown	No recurrence, 14 months
12	38/F	Perineum	8 × 3 × 2	Local recurrence, 1 year
13	37/F	Vagina	Unknown	No recurrence
14	63/F	Vagina	4 × 2 × 1	Local recurrence, 16 months
15	21/F	Vagina & pelvic floor	14 × 9 × 5	No follow-up
16	36/F	Vagina	10*	Local recurrence
17	47/F	Pelvic floor & vagina, rectum, labia majora	3 × 2 × 1	Two local recurrences, 4 and 12 years
18	30/F	Perineum & ischiorectal space	5·5	Local recurrence, 7 years
19	36/F	Vulva	8 × 5 × 5	No follow-up
20	32/F	Vulva	5 × 3 × 1	Local recurrence, 1 year
21	20/M	Perineum	Large	Local recurrence, 9 months
22	18/M	Perianal	4 × 2 × 2	No follow-up
23	27/F	Vagina	8 × 5 × 3	No recurrence, 1 year
24	15/F	Vulva	4 × 3 × 3	No recurrence, 1 year
25	49/F	Ischial region	9 × 6 × 5	No recurrence, 6 months

Cases 1–13 reported by Steeper & Rosai 1983
Cases 14–22 reported by Bégin *et al.* 1985.
Case 23 reported by Vaz-Romero *et al.* 1989.
Cases 24–25, present study
*Recurrent tumour.

sues. It may grow and occupy the whole pelvic region; invade paravaginal and pararectal spaces displacing pelvic structures and even extend into the retroperitoneum. In a case reported by Steeper & Rosai (1983) a large pelvic mass displaced the bowel, uterus and bladder and extended into the retroperitoneum.

The diagnosis of aggressive angiomyxoma is not usually made by the clinician but by the pathologist. The most frequent clinical diagnoses include vulvar mass, vulvar abscess, Bartholin's cyst, Gartner's duct cyst, vaginal cyst, vaginal prolapse or levator hernia. In the cases we report, the initial diagnoses were vulvar cyst and ischial lipoma.

Aggressive angiomyxomas often recur but do not metastasise. The recurrences may occur several years after first excisions, and long-term follow-up is necessary for these patients.

Since most tumours are locally invasive and because wide local resections are not always possible, most recurrences are likely to be related to inadequate original excision. In both of our patients, a second surgical excision was necessary. Because of the low mitotic activity it is unlikely that radiation therapy will prove to be a useful adjunct to primary surgical treatment.

In conclusion, aggressive angiomyxoma is a frequently misdiagnosed condition. A wide surgical excision based on a correct histopathological diagnosis is the basis of curative treatment.

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Necrotising granulomatous endometritis following endometrial ablation therapy

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Case report

A 46-year-old woman presented with a one-year history of menorrhagia. She had a normal size uterus, confirmed at a diagnostic curettage when tiny fragments of isthmic endometrium and a benign endocervical polyp were obtained. At follow up six weeks later, she continued to complain of heavy bleeding and was treated with danazol 200 mg bd in preparation for a transcervical resection of endometrium. Amenorrhoea was achieved and the endometrial resection was performed four months later.

Antibiotics were given postoperatively and two further courses were prescribed by her general practitioner as she complained of intermittent vaginal bleeding, persistent vaginal discharge and lower abdominal pain. The uterus continued to be very tender and, because of her symptoms, a total abdominal hysterectomy was performed two months after the endometrial resection.

The original transcervical resection specimen consisted of nondescript pale tissue of approximately 3 cm^3 in volume. Histological examination showed normal myometrium and inactive endometrium. The hysterectomy specimen received two months later weighed 127 g and was 9·9 x 5·5 x 4·5 cm. The myometrium was up to 1·7 cm in thickness and the endometrium up to 0·3 cm and was pale yellow in colour with focal haemorrhages.

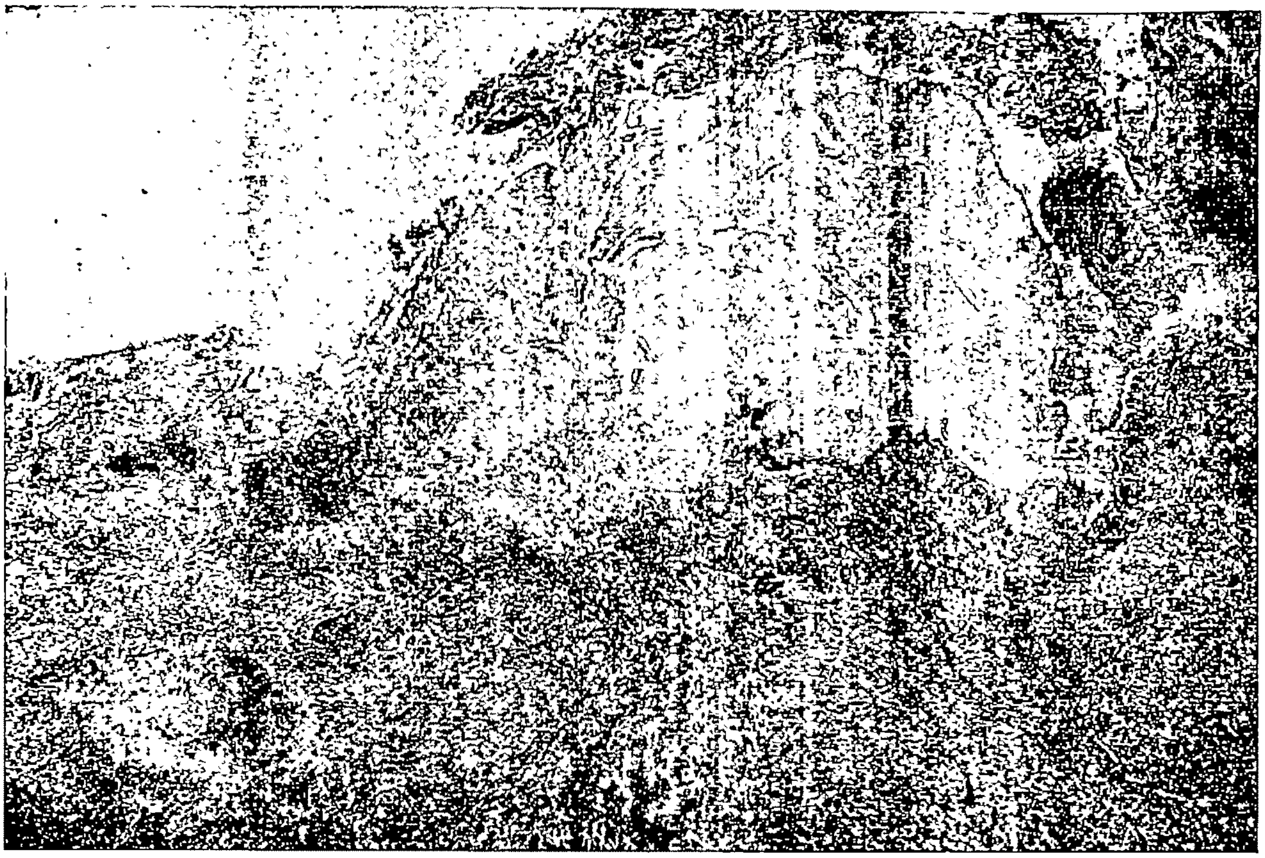

Fig. 1. Necrotic material (top) with ghost outline of vessels surrounded by palisading histiocytes and giant cells and smaller granulomata (bottom and middle left). Haematoxylin and eosin ×25

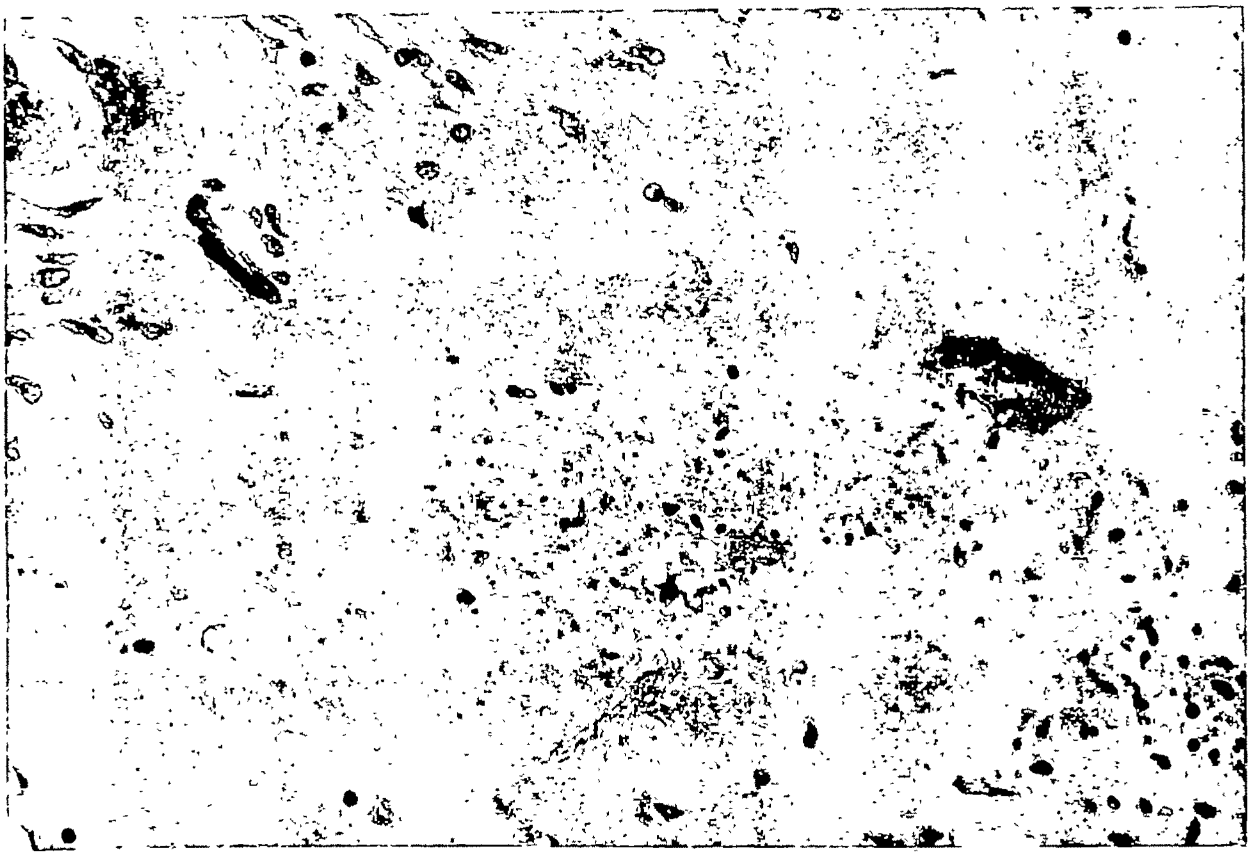

Fig. 2. Edge of granuloma demonstrating giant cells (top left) and charred material (middle right). Haematoxylin and eosin ×400.

The cervix and myometrium were normal on histological examination. The endometrial cavity contained eosinophilic necrotic debris in which ghost outlines of blood vessels could be seen together with streaks and small collections of neutrophils (Fig. 1). Strands of brown/black material were also present. The necrotic material was surrounded by a palisade of histiocytes with numerous Langhans and foreign body type, multinucleate giant cells (Fig. 2). Beneath this was a moderate inflammatory cell infiltrate consisting mainly of lymphocytes and eosinophils with occasional neutrophils. Fibrinoid change was seen in some arteries close to the inflammatory process. Stains for fungi and bacteria including tubercle bacilli were negative.

Discussion

Granulomatous endometritis is an uncommon condition with a differential diagnosis that includes tuberculosis, radiotherapy, mycoses, intra-uterine contraceptive devices, schistosomiasis, pin worm infestation, sarcoidosis, *T. mycoplasma* infection and granulomas associated with giant cell vasculitis (Buckley & Fox 1989).

Three cases of granulomatous endometritis have been reported recently which were thought to represent a reaction to injury following hysteroscopic ablation of the endometrium (Ashworth *et al.* 1991, Thurrell *et al.* 1991). Similar reactions are well recognised following transurethral resection of the prostate (Lee & Shepherd 1983) and have been described following diathermy ablation of endometriosis inthe peritoneum (Clarke & Simpson 1990) and in the cervix following surgery (Evans *et al.* 1984).

Transcervical resection of the endometrium is being used increasingly. This is our first case in which necrotising granulomatous endometritis has been seen in a hysterectomy specimen following transcervical resection We believe this to be only the fourth reported example of this condition after endometrial ablation therapy. As the use of transcervical resection grows, more cases are to be expected.

Although it is possible to confuse this condition with infective granulomas, there are features that allow histological differentiation including, in particular, the presence of golden brown intra- and extracellular pigment and the nature of the necrotic material in which ghost outlines of vessels are seen indicating that this is not a caseous type of necrosis. The presence of eosinophils and the irregular shape of the granulomas are also important diagnostic features.

It is important for the gynaecologist to be aware of this new entity and important for the histopathologist to recognise it. The pathologist must be made aware of a previous transcervical resection. This will prevent misinterpretation with an erroneous diagnosis of infective granulomas, for example, of tuberculosis as initially occurred in a previously reported case (Ashworth *et al.* 1991).

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SHORT COMMUNICATIONS

Under-reporting of medical terminations of pregnancy

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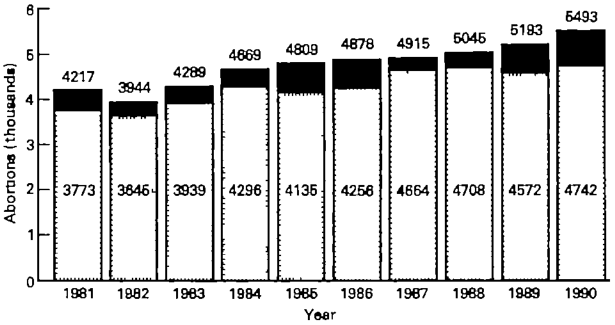

Fig. 1. Therapeutic terminations of pregnancy discrepancies between statistics obtained from OPCS (1981–1986)/KES (1987–1990) and the number of women having abortions in NHS facilities in NWRHA, 1981–1990. OPCS ■ excess KES

The Abortion Act 1967 permits termination of pregnancy by a registered practitioner subject to certain conditions. Regulations made under the Act require any such termination to be notified within seven days to the Chief Medical Officer. The Office of Population Censuses and Surveys (OPCS) undertakes the statistical processing and analyses of the notifications and publishes data regularly. Statistics on medical terminations are also available from hospital information systems. Since 1981 we have monitored the number of medical terminations of pregnancy recorded by hospital activity/Korner episode systems (KES) in this region and those formally notified to the Chief Medical Officer, and published by OPCS (Fig. 1). It is only possible to compare information on women resident in this region who have been treated in NHS hospitals in the region. OPCS will not provide data on District of treatment. In all years there were more cases reported from KES than from the statutory notification system; the excess varied from 251 in 1987 to 751 in 1990 (5·4% and 15 8%, respectively, of the OPCS notifications). We have checked whether the discrepancy was due to difficulties with the hospital information systems such as double counting, invalid diagnosis or inaccurate coding. After detailed analysis of KES for 1990, it seemed that double counting had occurred in 5 cases, less than 0·1% of the total. There were 92 cases where the diagnosis seemed inappropriate: 3 coded as normal delivery, one as fixation of bone of face, 88 with no procedure or operation recorded; these compromised 1·7% of all cases. The data administration department at the Regional Health Authority has well established procedures for auditing data accuracy. A random sample of records from several districts was audited; there were no coding errors in cases recorded as medical termination of pregnancy. It thus seems that, at most, the potential for the hospital information systems to include excessive numbers of medical terminations of pregnancy is of the order of 2–3%, and does not account for 13–14% discrepancy identified.

The age distribution was also compared. In 1990, the excess cases recorded in KES compared with OPCS data and expressed as a per cent of all KES codes was 11·4% in girls under 15, 10·7% in those aged 16–19, rose to 12 6%, 15·2% and 19·0% in women aged 20–24, 25–34 and 35–44, and fell to 16·7% in women aged over 45. This suggests an increase in under-reporting with maternal age. We conclude that the discrepancy is real. It is unlikely to be unique to the region.

The number of terminations of pregnancy is an important stimulus to concern about unplanned pregnancy (RCOG 1991) Our data suggest that the overall total may be 8–10% greater than that published by OPCS, and 20% greater for abortions in women aged 35 to 44.

Acknowledgments

The help of Mrs Michelle Williamson from the Regional Statistic Analysis Department, Mrs Mary Winney from Data Administration, and Mrs C. Beswick from typing services is gratefully acknowledged.

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Transvaginal versus transrectal sonography in postmenopausal women

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Ultrasound scanning of the pelvis is now a well accepted procedure in the evaluation of the postmenopausal endometrium and ovaries. Originally the transabdominal route was used, for example, to screen for early ovarian cancer (Campbell *et al.* 1989), and to measure endometrial thickness in patients with postmenopausal bleeding (Nasri *et al.* 1989). The recent introduction of transvaginal ultrasound scanning has permitted the use of higher frequency ultrasound at greater proximity to the pelvic organs, so providing superior resolution and overcoming the limitations of transabdominal scanning (Nasri *et al.* 1991*a*). However, the transvaginal route also has limitations, especially in virgins and patients with vaginal atrophy.

Transrectal sonography of the prostate gland was first used in the 1960s and 1970s (Takahashi *et al.* 1964; Watanabe *et al.* 1971) and has since become an important clinical tool in the diagnosis and management of prostatic cancer.

The present study was designed to compare the transvaginal and transrectal routes in the assessment of the postmenopausal uterus and ovaries and to determine whether the transrectal approach had advantages in this group of patients.

Subjects and methods

During a larger study of conservative management of women with postmenopausal bleeding, a group of 32 consecutive women with postmenopausal bleeding had transvaginal and then transrectal ultrasound scans using the same probe. Ultrasound examinations were performed with a Siemens Sonoline SL-1 (Sunbury-On-Thames, UK) with a multifrequency (5 and 7·5 MHz) mechanical sector transvaginal probe 5 MHz was employed for all examinations in this study. This has a scanning angle of 100 degrees and the point of maximum focus is 5 cm (range 2·5–7). The total length of the probe is 31·5 cm but the shaft length is 16 cm. The widest diameter of the probe footprint is 2·2 cm. The patient is examined transvaginally and then transrectally. The transvaginal scanning technique was similar to that described by Rottem and colleagues (1990). No special preparation is required for transrectal scanning. The patient is examined in the same position as for transvaginal scanning. The lubricated tip of the probe is applied to the anus, then advanced with a gentle, steady movement in the direction of the umbilicus. At 4–5 cm, a fall in resistance indicates that the rectum has been entered. This technique is similar to that used in sigmoidoscopy (Sleisenger *et al.* 1983). Systematic scanning of the pelvic organs is done in the same manner as transvaginal scanning. Figure 1 shows the difference in the direction of the probe during performance of transvaginal and transrectal scanning.

Results

Twelve patients experienced no strong feelings about either approach. Four preferred the transvaginal route and seven patients experienced more discomfort in the transrectal route; of these, three had external piles and one had a history of diverticular disease. The main discomfort was at the time of insertion of the probe. In one patient with an anal fissure the transrectal examination was not performed.

Transvaginal examination was not performed in four patients: three were virgins and one had had radiotherapy following hysterectomy and bilateral salpingo-oophorectomy for adenocarcinoma of the endometrium.

The technique provided equivalent diagnostic information of high quality in 27 patients (84%). Ovaries were seen by

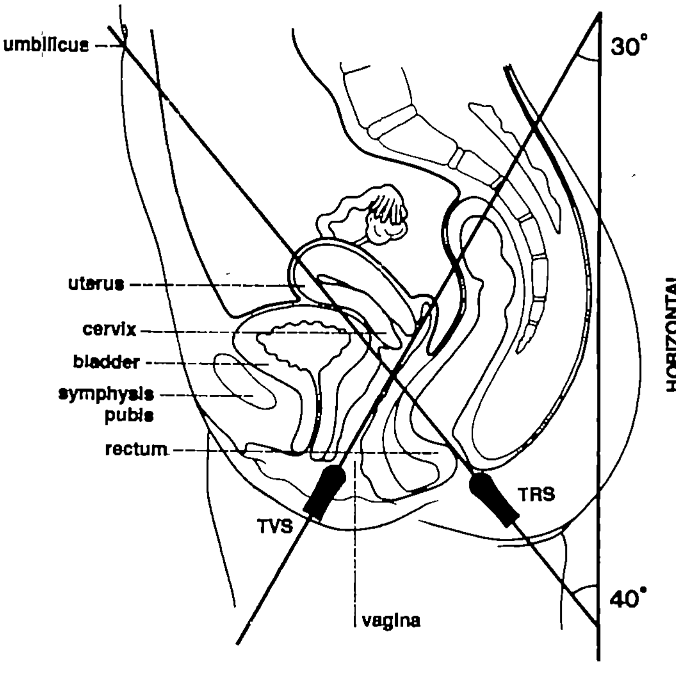

Fig. 1. A diagram showing the directions of both the transvaginal (TVS) and transrectal (TRS) probes during pelvic scanning. The transvaginal probe is aimed at the sacrum at 30 degrees to the horizontal plane. The transrectal probe is aimed at the umbilicus at 40 degrees to the horizontal plane

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both routes in 25 patients (78%), and by the transrectal route only in one virgin with ovarian carcinoma. The endometrial line was identified by both routes.

Discussion

Vaginosonography can be used as a screening procedure for early diagnosis of endometrial and ovarian cancer (Bourne *et al.* 1989; Osmers *et al.* 1990; Nasri *et al.* 1991*b*). The calibre of the vaginal probe renders examination difficult or impossible for some elderly postmenopausal women and virgins. This problem of limited access can now be overcome by the use of the transrectal route. The transrectal route does not present significant technical difficulties. In one patient of 86, the rectum was full. Extra gel placed both inside and outside the sheath overcame the extra shadows. No bowel preparation is needed. Transrectal examination is complementary to the transvaginal approach especially in postmenopausal patients. It is particularly useful in the group of women in whom transvaginal scanning may be contraindicated (i.e., heavy vaginal bleeding, especially in early pregnancy; suspicion of cervical incompetence, especially in patients presenting in early pregnancy; history of repeated early miscarriage; and evidence of stress or anxiety in respect of this type of examination).

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Current cup designs for obstetric vacuum extraction

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A large number of cup designs has been introduced since Malmström (1954) described his vacuum extractor. This makes it difficult to identify each cup by its proper name: in the Netherlands, half the obstetricians responding to a recent questionnaire concerning the use of vacuum extractor cups could not give the name of the cups they used. Also, authors of articles reporting assisted delivery are confused (Johanson *et al.* 1989).

Clinical trials have shown different results with the various cup models, in particular in relation to failure rates and the occurrence of neonatal scalp trauma. Recent reviews of published studies will aid the obstetrician in choosing a satisfac-

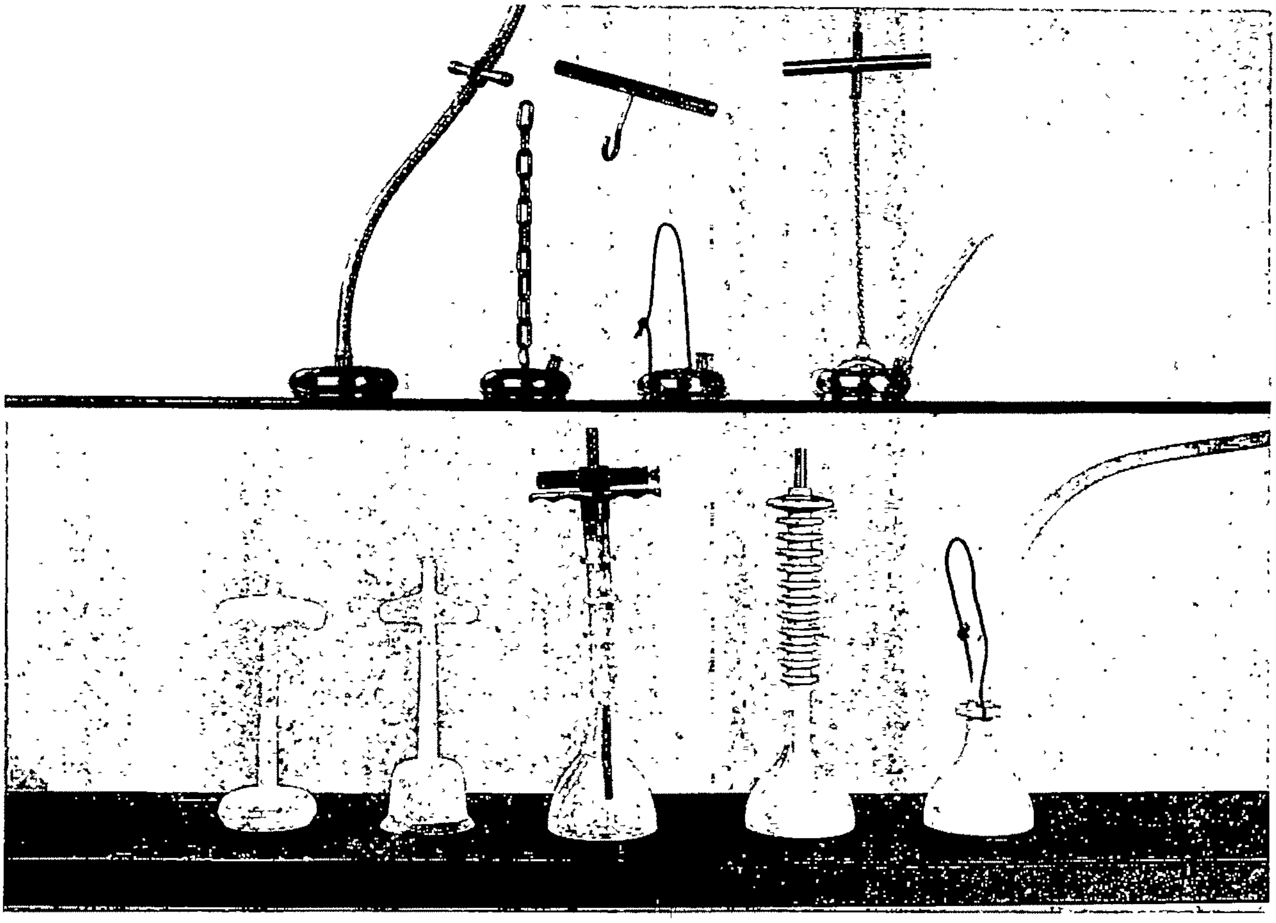

Fig. 1. Top row, left to right: the Malmstrom-type cup; the 'modified' cup by Bird, the 'new generation' cup by Bird; and the cup by O'Neil. The three cups on the right are OA (occiput anterior) models: the excentrically placed suction nozzle points upward If the suction nozzle is placed on the bulging side, pointing sideward, the cup is called an OP (occiput posterior) version. The metal cups are available with diameters of 40, 50 and 60 mm, except for the O'Neil cup which is only available with a diameter of 55 mm, the traction chains and traction handles may be at variance to the originals due to on-site modifications.

Bottom row, left to right: the disposable rigid 'new vacuum extractor' with a dome similar to the Malmstrom dome (50 mm diameter) (Paul *et al.* 1973) (*); the disposable pliable Mityvac cup (55 mm diameter) (Wood 1969) (*), the pliable Kobayashi or Silastic cup (65 mm diameter) with a valve, allowing ventilation (†); and two types of the pliable Silc cup, one with a traction handle (shown in 60 mm diameter, also available in 50 mm diameter) and one with a traction cord (60 mm only) (‡).

*Neward Enterprises Inc, PO Box 725, 91729–0725 Cucamonga CA, USA.

†Dow Corning Corporation, 48640 Midland MI, USA.

‡Menox AB, PO Box 6253, S-400 60 Gothenburg, Sweden.

tory cup (Vacca & Keirse 1989; Vacca 1990), but a concise illustration of the various cup designs has not been published.

For that reason we collected and photographed the various vacuum extractor cup models that to the best of knowledge are currently being used. The horn shaped cup by Finderle, that appears to be used in China (Liu & Beller 1987), could not be found.

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Cervical cone biopsy: a report of one hundred consecutive operations performed as day cases

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Cervical cone biopsy is a common gynaecological operation performed in the management of abnormal cervical cytology. In our own department, we perform approximately five such procedures each week. Traditionally the operation has involved a two or three night hospital stay, but day case treatment has been described previously in two series (Berkus & Daly 1980; Krebs 1984). Both these studies used cervical sutures to achieve haemostasis following conization. The principal early post-operative complication is haemorrhage. Rates as high as 13% have been reported, although post-operative complications have been shown to be related to the dimensions of the biopsy (Luesley *et al.* 1985).

Subjects and methods

The 100 cone biopsies reported were performed by experienced surgeons after previous colposcopic assessment. Cold knife cone biopsy was performed under general anaesthesia, following the application of Lugol's iodine to the ectocervix. Haemostasis was achieved by application of Monsel's solution to the cervical crater on a gauze pack (Gilbert *et al.* 1989). The vaginal pack was removed 4 h post-operatively. All patients were reviewed an hour later and allowed to return home unless overnight stay was clinically necessary, usually because of concern over vaginal blood loss. Histological findings were communicated by letter, and cervical cytology was performed 6 months post-treatment.

The patient characteristics are shown in Table 1.

Results

Sixty two (62%) women were discharged home the same day. There were four primary haemorrhages (4%): two women requiring further operative intervention in the form of cervical suturing and vaginal packing, and the other two needing vaginal packing alone. These four women stayed in hospital for two nights. A further 34 women were admitted overnight, including one woman who fell sustaining facial bruising, and one whose social circumstances did not permit her to return home the same day. The remainder were detained because of concern over the amount of post-operative vaginal bleeding. None of these women required further treatment and all were discharged home the following morning

Two women suffered secondary haemorrhage precipitating readmission — one after 7 days, the other after 10 days. Both women were treated with antibiotics alone and were discharged home after a 2-day hospital stay. None of the women treated required blood transfusion.

Discussion

We have been able to demonstrate that cone biopsy can be safely performed as a day case procedure for most patients. The frequency of primary haemorrhage in this series was low (4%), and all were detected within the post-operative observation interval. No woman was readmitted within 24 h of operation; the earliest readmission was 7 days after treatment.

Patients in whom there was concern regarding the amount

Table 1. Patient characteristics. Results are mean (range) values or number of women; data for age are median (range) value

Age	(years)	Parity	Cone diameter[a] (mm)	Cone length[a] (mm)	Primary haemorrhage	Overnight admission	Secondary haemorrhage
43 6	(21–68)	2·1 (0–7)	20 (9–35)	18 (4–30)	4	34	2

[a] Dimensions following fixation.

of post-operative bleeding were admitted overnight. However, in this group of patients (32 out of the 34 admissions) no further treatment was required. Analysing the 32 patients admitted overnight for observation of vaginal bleeding, 20 were among the first 25 women treated (80%) and only 12 in the last 75 (16%). This change probably reflects our increasing confidence in day care management.

In conclusion, we have shown that even with a conservative approach to discharge from hospital, most cone biopsies can be performed safely as day-care procedures. In addition, the use of day care facilities for the performance of cone biopsies has obvious financial implications, as well as being more acceptable to the woman.

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Editor: Diony Young, Geneseo, New York

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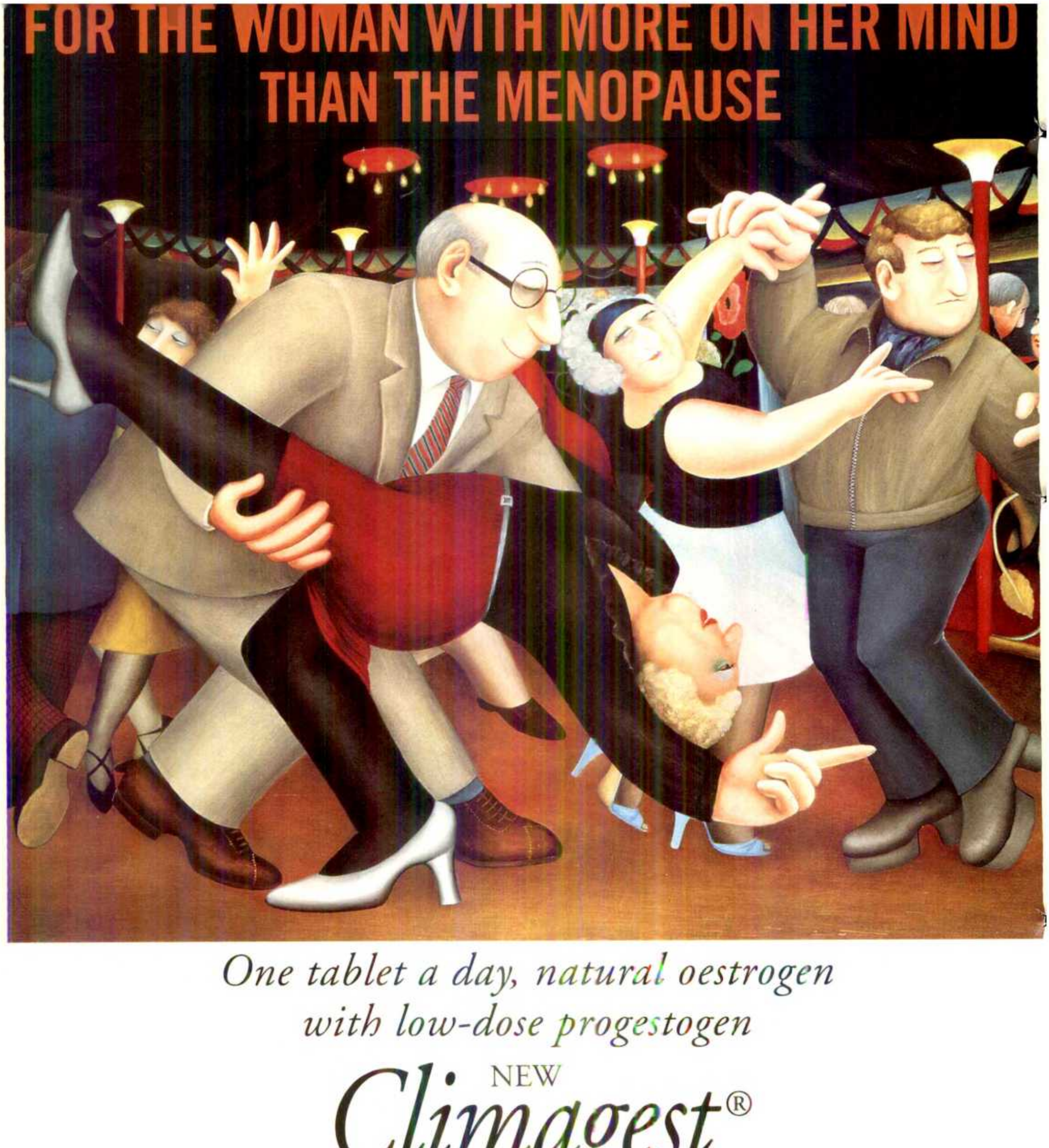

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British Journal of Obstetrics and Gynaecology
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CORRESPONDENCE

Incarceration of a bicornuate retroverted gravid uterus presenting with bilateral uretric obstruction

Dear Sir,

There are a number of points raised in the Case Report by Keating *et al.* (1972) that deserve mention.

They do not state the mode of anaesthesia administered to the patient. Given that the caesarean section was elective, in the sense that it did not necessitate a crash general anaesthetic, then surely an epidural would have been safer for the patient, but more to the point, would have enabled the surgeon/s to discuss the findings with the very young woman they were about to hysterectomize.

Assuming that the principal operating surgeon was a consultant (and if not, why not?), then why proceed to hysterectomy at all? I understand from the tenor of the letter they rightly discovered the acute retroversion intra-operatively and hence were able to delineate the surgical incisions made. That being the case I cannot see any reason to doubt 'the integrity of the suture lines.' Any operating surgeon familiar with pelvic anatomy and the principles of healing will know well how quickly the female pelvis tolerates such insults on the path to full and normal recovery.

There was a pelvic mass, granted, but given the gravity of the surgery subsequently performed then surely a biopsy, or even a frozen section, with possible recourse to a laparotomy as an interval, would have been the most appropriate management. Malignant uterine causes of the findings in this age group are very rare indeed.

As it now stands a 19-year-old woman has been hysterectomized for an uncommon, but totally benign condition, with the high probability of a premature menopause given the loss of the ascending branches of the uterine arteries that are a vital part of ovarian blood supply.

Euan Laird
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References

Keating P. J., Walton S. M. & Maouris P. (1992) Incarceration of a bicornuate retroverted gravid uterus presenting with bilateral uretric obstruction. *Br J Obstet Gynaecol* **99,** 345–347.

Authors' reply

We read with interest the comments of Dr Laird and would agree that the decision to perform a hysterectomy (not hysterectomize!) on a 19-year-old is not one to be taken without full consideration. Unfortunately, a general anaesthetic was used but this was at the patient's request and in retrospect, having the patient awake during such an ordeal may have been psychologically traumatic, the obtaining of objective consent far from possible.

Dr Laird fails to appreciate the sequence of events leading to the delivery of the baby, otherwise he will appreciate that the incisions inflicted, first through the anterior vagina, then the posterior vagina and finally transversely through the fundus of the uterus were far from 'delineated.' The anatomy only became clear after delivery, by which time the uterus was not attached to the vagina (it having been completely circumcized) and the integrity mentioned would have been following reattachment. The decision to proceed to hysterectomy was taken by the patient's own consultant (S. M. W.) but only after a second consultant had been called into theatre in order to discuss the pathological findings. Although taken into consideration, the 'tumour' played only a small part in the decision and at no time was malignancy suspected. Frozen section if available would not have helped.

Having made sure that our patient had a live healthy baby, our main concern was the health of the mother with a worsening renal condition, whilst reducing immediate morbidity and guarding against obstetric disasters in the future. Hysterectomy offered the only solution and any obstetrician in the same position would have difficulty in finding a safe alternative, despite the unfortunate effect of leaving a 19-year-old without a uterus.

Dr Laird, in his comments, shows a singular lack of concentration on the issues involved or insight into the considerable discussions that occurred before such decisions were made.

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P. Maouris
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Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean

Dear Sir,

Having worked in West Africa I was interested in Lelia Duley's (1992) paper and would like to make two comments. Firstly, Ms. Duley is obviously aware of the difficulties in obtaining accurate data on maternal mortality but it continues to worry me that 'pockets' of extremely high maternal mortality exist unbeknown to the WHO database. For example Ghana's MMR is quoted as 670/100 000 whereas it was 1700/100 000 in the hospital in which I worked (Fiander 1991). The worst maternal mortality scenarios affect the least privileged and the most isolated of the world's women and their plight deserves documentation. In this respect could not the WHO set up a 'notification procedure' by which health workers could report their local experience?

Secondly, it is my observation that the problem of hypertensive disease varies between geographical areas within a country such as Ghana. For example, hyertensive disease was an important cause of maternal mortality in the more southern tropical rain forest regions but I rarely saw pregnancy-related hypertension and never saw eclampsia in the northern savannah regions. Obviously environmental, ethnic or dietary factors must be operating either by preventing or facilitating hypertensive disease. These require further investigation and evaluation as they may have important implications for the prevention of maternal death.

As Ms Duley concludes 'how to reduce deaths associated with hypertensive disorders of pregnancy will not become clear until there is better evidence than is currently available.'

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Duley L. (1922) Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. *Br J Obstet Gynaecol* **99,** 547–553.

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Which hormone tests for the diagnosis of polycystic ovary syndrome?

Dear Sir,

In their report of endocrine findings in women with polycystic ovary syndrome (PCOS), Robinson *et al.* (1992) refer to ultrasound as the gold standard for the diagnosis of PCOS, and suggest that hormone investigation should be used to provide confirmatory evidence. While pelvic ultrasonography has proved to be an invaluable method for the study of women with polycystic ovaries (PCO), we believe its application in routine clinical practice is not without problems.

The characterization of ovarian morphology using ultrasound requires considerable expertise and experience beyond the comparatively simple requirements for the diagnosis of ovarian tumours and for the monitoring of follicular growth. Orsini *et al.* (1985) reported that only one third of 16 patients with laparoscopically-diagnosed PCO had evidence of increased follicularity at transabdominal ultrasonography. El Tabbakh *et al.* (1986) similarly studied 20 women with laparoscopically-diagnosed PCO and found that no follicles were discernible in 11 cases. Studies comparing pelvic ultrasonography with magnetic resonance imaging for the examination of ovarian morphology in women with PCOD diagnosed biochemically also indicated that abdominal ultrasound fails to reveal many of the smaller follicles (Faure *et al.* 1989). This difficulty in defining small follicles helps to explain the differences in the criteria used to diagnose PCO reported by different groups.

Apart from any limitation of ultrasonography in the definition of ovarian morphology, it must be remembered that the method is limited to the morphology of the ovary. The finding of PCO is misleading in a small proportion of cases because the true cause of oligo-amenorrhoea will be overriding any disorder that might occur due to (pre-existing) PCO. We, and others (Conway *et al.* 1989), have found PCO at scan in women with hypothalmic disorder related to weight loss, and hyperprolactinaemia due to a pituitary adenoma. The danger of largely basing the diagnosis of PCOS on ovarian ultrasonography is the possibility of overlooking serious conditions such as anorexia nervosa, which may be difficult to detect in practice.

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Faure N., Prat X., Bastide A. & Lemay A. (1989) Assessment of ovaries by magnetic resonance imaging in patients with polycystic ovarian syndrome. *Hum Reprod* **4,** 468–472.

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Robinson S., Rodin D. A., Deacon A., Wheeler M. J. & Clayton R. N. (1992) Which hormone tests for the diagnosis of polycystic ovary syndrome? *Br J Obstet* **99,** 232–238.

Authors' reply

Dear Sir,

We were interested in the letter by Robert Fox, and agree that the use of pelvic ultrasonography in routine clinical practice can be problematical. However, we have found that with well-trained experience ultrasonographers there is little difficulty in differentiating polycystic and normal ovaries. As regards the question of failure of ultrasound to identify PCO in laparoscopically diagnosed cases the correspondents have not cited a recent publication from Saxton *et al.* (*Br J Obst Gynaecol* 1990, **97,** 695–699), cited in our report, which showed a very good (91%) specificity of ultrasound. This is even more evident with routine use of transvaginal ultrasound. We believe that ultrasound, in experienced hands, can be used as the gold standard for defining ovarian morphology. Nevertheless, we agreed with the view expressed that not all women with oligomenorrhoea, hirsuitism and biochemical hyperandogenism who clinically are classified as polycystic ovary syndrome will have polycystic morphology of the ovaries. We accept that hyperprolactinaemia may produce a similar morphological appearance on ultrasound but this rarely causes diagnostic difficulty since the biochemical findings are of low oestradiol and testosterone levels, which is also true for hypothalamic amenorrhoea. Therefore, if all features, clinical, biochemical, and ultrasound are taken together there is little difficulty in distinguishing PCOS from other causes of oligo-amenorrhoea. We clearly state that in our study hyperprolactinaemia was excluded, and none of the subjects presented with weight loss related amenorrhoea.

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BOOK REVIEWS

Modern Approaches to Endometriosis edited by Eric Thomas & John Rock., Kluwer Academic Publishers, Dordrecht, Boston, London, 1991, 302 pages, fully illustrated, with figures and tables, £40.00.

Modern Approaches to Endometriosis has been written by a collection of recognized experts in the field from Europe and the United States of America. The book is divided into two parts—the first on Scientific Aspects of Endometriosis and the second on Clinical Aspects of Endometriosis.

Current understanding of the pathogenesis, aetiology and significance of this enigmatic disease is not yet resolved and in view of this the authors were asked to be more speculative than normal in their chapters. In general, this has been adhered to and very few of the authors have made definitive statements without data to support their comments.

The first section is an excellent, thorough and up-to-date review of the theories and scientific understanding of endometriosis, including reviews on pathogenesis, steroid receptors, the peritoneal environment, the immune system, endometrium and endometriotic implants. One of the editors, Eric Thomas, concludes this section by examining the relationship of endometriosis and infertility. His critical review of the literature suggests there is no evidence to support a casual relationship in the absence of peritubal or periovarian adhesions, nor proof to recommend medical or surgical treatment to benefit future fertility. In fact, only Dmowski persists in the belief that treatment may result in improved reproductive performance in mild disease.

Much of the discussion on the surgical treatment of endometriosis, in the second part of the book, has been written by American authors and therefore does not always concur with British opinion or practise. The chapter on laser therapy is an excellent review of the current value of this treatment option and the various drug therapies available are adequately appraised. The inclusion of data from Henderson & Studd supporting pelvic clearance for definitive surgery is important, but it is a little disappointing that they limit the majority of their discussion on hormone replacement therapy to oestrogen implants which are themselves a matter of controversy.

This book is written in a most readable style and is a wonderful up-to-date review of the current understanding of the scientific and clinical aspects of endometriosis. It will especially appeal to anyone with an interest in the subject, but should equally be of benefit to any general gynaecologist wishing further knowledge or reference on the subject.

Gillian L. Rose

Law Reform and Human Reproduction edited by Sheila A. M. McLean. Dartmouth Publishing, Aldershot, 1992. £35.00.

The appearance of this well-produced and amply referenced book will certainly be welcomed in the appropriate quarters.

The text, ably edited by Professor Sheila McLean, consists of ten chapters written for the most part by an international panel of senior academic lawyers. With two exceptions, each chapter takes readers through the development and present status of the law governing human reproduction in different jurisdictions ranging through Europe, the Americas and Australasia, including in one chapter devoted to 'policy and procreation', reference to relatively obscure population pockets of the third world. Each chapter is liberally sprinkled with case citations, Acts of the legislature and in one, an apt attribution to holy writ! Of greatest interest to readers in the UK is chapter 7, written by Norrie, which includes commentary on the Human Fertility and Embryology Act of 1990; unfortunately it does not touch upon a glaring imperfection contained therein, which until amended effectively precludes the normal communication between consultants and general practitioners for so long a corner stone of traditional British medical practice.

In conclusion, I do not feel that this relatively expensive book is one for the generalist gynaecologist or for aspirants to higher degrees and diplomas—it is essentially a text for lawyers and ethicists; having said this, it should certainly be available in specialized assisted reproduction clinics and to the ethics committees that advise them.

C. J. Orr

Assisted Vaginal Delivery by Leonard E. Laufe & Michael D. Berkus. McGraw-Hill Inc, New Jersey, 133 pages, including figures and tables.

This book has two complementary sections. The early chapters are a critical appraisal of the evolution, design and functions of obstetric forceps and ventouse, the message being that there is a lot to be learned from history. There is a surprisingly lack of comment on the all-important cephalic curve.

The second half is essentially a 'bench book'. There are clear sets of ground rules with descriptions of assessment, choice of instrument and clearly written step by step guidance for use in differing circumstances, appropriately tempered with caution. Because each section is self contained the text tends to be repetitive but is none the worse for that. Unexpected omissions include the choice of anaesthesia and the management of the bladder.

The book has an essentially American bias and many of the instruments described would be unfamiliar to United Kingdom readers. The ACOG classification is used to avoid misunderstandings in the use of the terms 'outlet', 'low' and 'mid-cavity'. Generally long forceps are favoured, even for outlet deliveries, and there is a preference for instruments with solid blades with the Luikart modification (hollowed on the inner surface). Pajot and Scanzoni manoeuvres are described in detail.

I see this book as a valuable addition to a departmental library, not as a do-it-yourself manual, but as a compendium of useful and interesting information to provide a background for stimulating discussions at staff meetings and in postgraduate teaching.

Bryan Hibbard

Primary Care of the Preterm Infant edited by Judy C. Bernbaum & Marsha Hoffman-Williamson. Mosby Year Book, St Louis, Baltimore, Boston 1991. 344 pages with figures and tables. £25.50 soft cover.

Too often there is the temptation, when the *sturm und drang* of intensive care has given way to the relative calm of special care, to regard the recovering preterm baby as 'merely a grower'. Housed in a corner of the special care nursery or transferred back to the referring hospital, the baby is often handed over to the care of a junior doctor who did not know him in the 'acute' phase and the baby's very particular needs may be neglected. Then, with sighs of relief all round and a box of chocolates to the neonatal unit, the baby is discharged home to the care of parents—who may or may not now be experienced—and a GP and health visitor who will probably not have been previously involved, and who may not be quite up-to-date with the latest neonatal developments and who may be very unsure of what to expect. With the advancing trend to sending babies home earlier the primary health care team may be faced with a small baby on home oxygen and electronic monitoring, with a ventriculoperitoneal shunt *in situ* and on a cocktail of vitamins and feeding supplements.

The bewildered team can do no better than to turn to this book for help. It is full of accurate information and sensible advice. It is readable and clearly set out with helpful checklists, appendices, references and reading lists. It deals with the discharge and follow up of normal preterm infants as well as covering those with complications. There are excellent and up-to-date chapters on the medical management of chronic lung disease, CNS complications, gastrointestinal issues and problems of vision and hearing. There is detailed information on growth expectations and nutritional needs as well as advice on immunization schedules and developmental surveillance. The well-illustrated chapter on common physical scars of prematurity will also be found useful. There is a substantial section on neurodevelopmental outcome with helpful tables and illustrations, and a final section dealing with family and social issues.

My quibbles are few. As this is a North American publication there is little information relevant to the UK on liaison workers, clinical support services and parent support groups. Overall not much has been omitted but perhaps a section on bereavement, coping with multiple pregnancies and with very severely disabled infants, e.g., those with a chromosomal abnormality might have been included.

This is an excellent book; it should be read by neonatologists, and general and community paediatricians of all seniorities as well as by general practitioners, health visitors, liaison nurses and all involved with the survivors of neonatal intensive care.

The depth and breadth of the appeal of this book is perhaps best illustrated by the acclaim given to it in the foreword—whose writer is both a Professor of Paediatrics and the parent of a preterm baby.

P. Hamilton

Obstetrics: Normal and Problem Pregnancies edited by Steven G. Gabbe, Jennifer R. Niebyl & Joe Leigh Simpson. Churchill Livingstone, New York, Edinburgh, London, 1991, 800 pages, illustrated, £65.00.

This 800-page, well-illustrated and well-referenced book has been written by over 40 different contributors. In section I, there are seven chapters on anatomy and physiology related to obstetrics which were well written and provided sound scientific basis for the practice of obstetrics. The several chapters are well illustrated with diagrams which undoubtedly helps readers to go through these otherwise 'heavy' chapters with relative ease.

The six chapters on pre-natal care in section II emphasize preconception care, genetic counselling, obstetric ultrasound and antepartum fetal evaluation. However, one weakness of this section is the relative lack of discussion on the management of some conditions which are not uncommon as microcephaly, macrosomia and gastroschisis.

In section III, there are seven chapters devoted to intrapartum care. They are generally well written, but it was disappointing to find that there was little mention of cephalo-pelvic disproportion, its diagnosis and management. Malposition was not even found in the index, despite a whole chapter being devoted to malpresentation.

It is appropriate to include two chapters on postpartum care and these are adequate. The seven chapters on complicated pregnancies were very well written, particularly those on ectopic pregnancy, preterm birth and multiple gestation. There were up-to-date discussions on common issues of management which are of invaluable help to practicing obstetricians.

Section VI was devoted to pregnancy with co-existing disease. The chapter on hypertension was adequate. It is somewhat disappointing that the chapter on haematologic diseases did not cover thrombosis and the management of patients at risk of thrombo-embolism in the anterpartum period.

Overall, despite a number of omissions, this is a comprehensive and well written textbook which I think it should be read by the practicing obstetricians. It is certainly worth having one in departmental libraries.

T. C. Li

Books received some of which may be reviewed at a later date:

A Textbook of In Vitro Fertilization and Assisted Reproduction edited by Peter R. Brinsden and Paul A. Rainsbury. Parthenon Publishing, Lancs, 1992, 451 with figures and tables, £58.00.

Atlas of Transvaginal Surgery edited by Shlomo Raz MD. W. B. Saunders, Philadelphia, PA, 1992, 262 pages with figures and tables, £78.00.

Basic and Clinical Biostatistics edited by Beth Dawson-Saunders & Robert G. Trapp. Appleton & Lange, Norwalk, CT, 1992, 320 with figures and tables.

Essential Obstetrics and Gynaecology edited by E. Malcolm Symonds. Churchill Livingstone, Edinburgh, 1992, 341 pages with figures and tables, £19.95.

Ethics and Reproductive Medicine edited by David R. Bromham, Maureen E. Dalton, Jennifer C. Jackson & Peter J. R. Millican. Springer-Verlag, Berlin, 1992, 288 pages with figures and tables, DM 118.000.

Fetal Behaviour—Developmental and Perinatal Aspects edited by Jan G. Nijhuis. Oxford University Press, Oxford, 1992, 273 pages with figures and tables, £35.00.

Fetal and Neonatal Physiological Measurements edited by H. N. Lafeber, J. G. Aarnoudse & H. W. Jongsma. Elsevier Science Publishers, Amsterdam, 1992, 322 with figures and tables.

Hysterosalpingography edited by David J. Ott & Jamil A. Fayez. Urban & Schwarzenberg, Baltimore, Munich, 1991, 130 pages with figures, £43.00.

Medicine of the Fetus & Mother edited by E. Albert Reece, John C. Hobbins, Maurice J. Mahoney & Roy H. Petrie. J. B. Lippincott Company, Philadelphia, PA, 1992, 1632 with figures and tables, £145.00.

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COMMENTARIES

Euthanasia in gynaecological oncology

Dying is a complicated human behaviour. There are not only several stages in the process of dying, but in each stage the dying person can attach different values to this process. To understand these changes, one must be emotionally close to the person who is dying. This means that terminal care can only be given by those who know and understand the patient (Hilhorst 1980). Terminal care means everything that is done for the terminal patient in her last phase of life by a third party in order to help and to support her to the end, and medical care has to include a consideration of euthanasia (Hilhorst 1980).

The word euthanasia comes from the Greek word *'eu thanatos'* which means good death. The commonly used definition of euthanasia is as follows: Euthanasia is understood to mean a deliberate life-shortening medical act performed on a seriously ill patient at her/his express wish. Interest in the problem of euthanasia has increased during the last years. Dying has become a process that can be manipulated and can be dignified as well as undignified; it can be lengthened or made shorter, it can be made easier or more difficult.

It is very difficult to obtain hard facts about the incidence of mercy killing. The numbers of death by euthanasia in the Netherlands have not been known until recently, with much ill-founded speculation in the past (Fenigsen 1989). Opinion polls in the Netherlands indicate a developing liberalisation and acceptance of mercy killing in this society. Recently, a Dutch nationwide study of euthanasia and other medical decisions concerning the end of life has been published by Van der Maas *et al.* (1991); euthanasia by the administration of lethal drugs is reported to have been associated with 1·8% of all deaths.

Every doctor has to develop his own view of this problem and this is especially necessary for oncologists. In discussions about euthanasia there are two conflicting, and incompatible, view points:

Human life has an absolute value. This stance is mostly prescribed by religion and is in itself absolute. Concessions are not possible and the stance has a collective character in that the protection of human life has to be guaranteed by the authorities for the entire society.

The more liberal stance states that a human being has in all or some circumstances a right of self determination over his/her own life. This stance is not absolute nor collective but individual.

Discussions about euthanasia between those holding these view points are useless but within the second discussion makes great sense.

Euthanasia, or mercy killing, is forbidden in all countries by law. In the Netherlands Sections 293 and 294 of the Criminal Code dated 1886 read as follows:

Section 293: The person who on the clear expressed and serious request of another person takes that other person's life will be sentenced to a maximum of 12 years imprisonment.

Section 294: The person who deliberately incites another person to suicide or who helps or provides him with the means to do so will, if suicide follows, be sentenced to a maximum of 3 years imprisonment.

In the Netherlands all deaths have to be reported, the doctor responsible reporting whether the death was natural or not. For a 'not natural death', the law requires that the public prosecutor investigates whether a penal offence has been committed. If necessary he can order an arrest and bring charges, and permission for the burial or cremation is given only after the investigation.

A distinction is made between the written law and the living law in which the latter is more in accord with the spirit of the time and is an interpretation of the written law. This is happening with mercy killing. Informal surveys show that euthanasia is practised on a broader scale than had been assumed and that any mercy killings are reported as natural deaths. In those cases that have been brought to court, charges were mostly either dropped or a symbolic sentence was given. So far, in-depth discussions in society and in Parliament have not led to a change in the Criminal Code and mercy killing remains a crime, in spite of being accepted by a majority of the people, a majority in Parliament and a majority of the medical establishment.

To overcome the discrepancy between written and living law, 25 precise criteria have been formulated by the Royal Netherlands Society of Medicine and in jurisprudence. After euthanasia, the doctor must report the death as an 'unnatural one' to the authorities. An official report is made by the criminal investigation department and is sent to the regular meeting of the Attorney General chaired by the Minister of Justice. In the report the doctor can appeal to *force majeur*, which means that the wish of the patient brought him to a situation where his medical duty to help the patient brought him in conflict with the law. This report will be checked in relation to *force majeur* and for 25 precise criteria. On the basis of this report the authorities will decide if the doctor will be prosecuted or if the case will be dismissed.

The most important criteria for the tolerability of euthanasia are:

—The patient requests euthanasia on his/her own free will.
—The patient requests euthanasia repeatedly.
—The patient is sound of mind.
—The medical prognosis is hopeless and certain to result in death.
—The decision is made by a team of closely involved doctors, nurses and carers.

—The hopeless prognosis and certainty of death is verified by an independent physician who is not involved in the treatment of the patient.

If possible the wish of the patient is written down in a codicil which he/she signs and which is added to her case file.

In a letter to Parliament the government has defined several situations that are considered to be normal medical practice and not euthanasia. These situations that are considered not to fulfil the criteria of euthanasia are:

—Not starting a treatment or ceasing a treatment on the express and serious wish of a patient.

—Not starting a treatment or ceasing a treatment in those cases where, according to the prevailing medical view, such a treatment is useless.

—Medical action that is necessary for and in its nature directly intended to the relief of serious suffering, even though this action has a consequence of making death occur more easily.

The application of those criteria has the result that the concept of passive euthanasia has ceased to have official significance and that euthanasia now means the active causation of death.

The process of euthanasia

Most cancer patients are told, or realise themselves, that they cannot be cured and that they are going to die. During the first 'bad news talks' it is often apparent that they fear the final phase of life. Only when a relationship based on mutual trust has been built up can this fear be discussed. Often the patient speaks about what she does *not* want: no unbearable pain, not being connected to all kind of tubes and apparatus, no life prolonging measurements.

If she discovers that these fears can be discussed, she may sometimes express the wish for euthanasia. The request for euthanasia often has to be interpreted as an expression of the inner need to maintain a sense of intactness as an individual and of personal control over events (Hilhorst 1980). The simple fact that this possibility is not rejected directly gives much rest and confidence. For the patient this means that her doctor is her ally during her last phase of life. As Van der Maas *et al.* (1991) reported, two thirds of these requests never result in euthanasia since physicians can often offer alternatives.

In general, four factors are important in euthanasia (Hilhorst 1980):

1. **The condition of the patient:** Is doctor–patient communication adequate? Is it possible for her to have an accurate overall overview of the situation? In this context effective pain relief is important. Quite frequently good palliative care and adequate analgesia make euthanasia unnecessary.

2. **The wish of the patient:** The doctor must assess carefully to what extent the patient wants any further treatment and to what extent this treatment makes sense as palliation.

3. **The wish of the family:** If the family relationships are good, the wishes of the patient can be assessed in the context of the family. When the opinion of the family does not fit with the wish of the patient, the opinion of the family must play a minor part.

4. **The opinion of the team in attendance:** The opinion of the team in attendance finds its best expression in group conversations with all persons concerned. In the practice of gynaecological oncology, this means discussions in which nurses, colleagues, and, if necessary, a social worker, a pastor and preferably the family practitioner of the patient participate. The request of the patient is discussed within this team. The most important task of such a team is not to make a value judgement about the request of the patient but to ensure that the necessary caution is exercised during the decision making.

Finally the team has to decide if the euthanasia can take place or not. Important conditions are that nobody has to participate in euthanasia against his or her conviction, and the euthanasia has to be performed by the doctor in attendance. Ideally this is the doctor who has supported the patient during her illness.

In our experience there are several factors that can hinder adequate decision making in euthanasia. These include:

—A lack of information or conflicting information. This situation can raise resistance in the team and can finally lead to a refusal to cooperate in the process of euthanasia.

—A lack of knowledge of the problems of terminal care. For this reason it is important to educate inexperienced doctors and nurses in this field.

—Nurses who are too young and who as a consequence cannot cope emotionally with the problem of euthanasia.

—A lack of personnel resulting in a shortage of attention for the terminally ill patient.

—Frequent changes of personnel during days, nights and weekends, leading to a lack of identification with the patient.

—Nurses allocated to evening and night shifts who are insufficiently informed about the situation.

—*Ad hoc* policy during evening and night shifts or during the weekends because the attending physician is absent.

To minimise the adverse influence of these factors, the attending physician, as the one who has to look after the interest of the patient, has to ensure an optimal exchange of information on the ward and within the team. Preferably he or she is on call for this particular patient during nights and weekends. In this respect it must be realised that a request for euthanasia never comes unexpectedly. Usually the possibility has been discussed previously several times and, in my experience, most patients plan ahead and ask for euthanasia on a particular day and hour. To be able to give all the attention needed to the patient and the family I usually suggest to the patient that the euthanaticum be administered at the end of the day or during the weekend. The advantage of this planning is that no-one is hindered by daily duties and by the business of the ward.

Technique of euthanasia

Through the years several methods of euthanasia have been developed which can be administered orally as well as intravenously. Shortly after administration of the drugs the patient loses consciousness, duration of dying being dependent on type and dosage of drug. For example, keeping the patient in a deep sleep will result in a process that can take several days. The administration of barbiturates can reduce this process to minutes or hours. In my personal experience, the process of dying should not take too long and should be initiated at a predetermined time. The advantage of this approach is that everybody can pay much attention to the process of taking leave: of the family, of the dying and of the aftercare of the family. Dying unexpectedly, just after the family has left for a while, or just at the moment that the attending physician or closest involved nurse are not available, cannot happen with this method and forms the most important disadvantage of the slow method. It is also my experience that patients often want to be informed about the methods available. Many of them express the wish not to be kept in the 'chemical coma' for hours or days and prefer to die soon after they are unconscious.

The following case illustrates the process that leads to euthanasia. Patient A is a 28 year old unmarried Roman Catholic woman with no children. Two years after radiotherapy elsewhere for a cervical carcinoma stage 2B, she consulted our clinic with an inoperable pelvic recurrence of her disease. Curative treatment was not possible. Palliative chemotherapy was rejected because of low response rates and the serious side effects. Since her main complaint was pelvic and low back pain, adequate pain killing medication was prescribed. During close follow up, the patient repeatedly expressed her wish to have euthanasia as soon as she judged that quality of her life was not acceptable. The patient also discussed this wish with her mother and her brothers and sisters. Increasing pain made the administration of morphine necessary and, later, admission to the hospital. Effective pain killing was achieved by a continuous epidural anaesthesia. At this point the patient considered that her time had come. Her clearly stated wish was discussed extensively by a team composed of the attending physician, the head of the department, the head nurse, the attending nurses and the social worker. Because her prognosis was hopeless, the team decided to grant her request. The patient did not want the process of dying to take a long time and asked for a quick method. The patient and her family wanted to be together during the administration of the drugs. Together they asked to have the euthanasia performed on a Saturday morning. In the presence of her family and after having taken leave of everyone personally, the drugs were administered intravenously by the attending physician. She died after a few minutes. The laying-out of the body was taken care of by the nurse assisted by two of her sisters. The attending physician stayed with the family in another room until the laying-out of the body was completed.

Six weeks after the funeral, the process of euthanasia was evaluated with the family. Everyone felt that the right decision had been taken. Despite the sorrow they felt about the loss of a beloved member of the family, all were grateful that the woman had not been forced to endure useless suffering.

Conclusion

In discussions concerning euthanasia, much attention is paid to legality and to technique. However, the emotional burden assumed by the doctor is also important; he/she performs an art that directly finishes someone's life. In my personal experience, one can only proceed to this action if a good mutual relationship has been developed with the patient. The consequence of this relationship is that one becomes involved in the process of taking leave and mourning. This can ask very much of the doctor, especially because one has to give priority to the duties of a physician. Sometimes the opinion is expressed that euthanasia is too easy a solution for a difficult problem and can be avoided by adequate terminal care. In my opinion the contrary is true. The euthanasia requires great preparation with the patient and her family and can take place only as a part of terminal care which is given with much effort and personal concern.

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Pelvic inflammatory disease

Microbial invasion of the female upper genital tract may result in pelvic inflammatory disease (PID). This is a complex condition and our understanding of the epidemiology, microbial aetiology and pathogenesis is limited. Furthermore, the disease process may be occult or overt, making clinical diagnosis far from straightforward. Optimal therapy that not only eradicates infecting micro-organisms but also preserves reproductive function and prevents long term sequelae has yet to be defined.

For over 30 years, epidemiological data from industrialised countries has demonstrated an increasing incidence of PID. This has paralleled a rise in cases of sexually transmitted disease suggesting that a majority of cases of PID are caused by sexually transmitted micro-organisms. The available data to determine the basis for treatment and prevention regimens in the United Kingdom are limited. There are two sources of data: (1) returns to the Department of Health from genitourinary medicine (GUM) clinics (Department of Health 1991) and (2) Hospital Inpatient Enquiry data (Office of Population Censuses and Surveys 1989). Most cases of PID are diagnosed on clinical grounds alone with the inherent risk of over-diagnosis owing to the lack of specificity of symptoms and signs. Not included in the reported data are the cases treated by general practitioners (probably those with milder symptoms), and those treated as outpatients or in private practice. Women with atypical or silent PID who do not present, or are misdiagnosed, are also not included. Therefore, any assessment of incidence is inaccurate, probably underestimating the true number of cases. Notwithstanding these deficiencies, the trend for acute PID based on hospital discharge data continued to rise throughout the early 1980s with a 50% increase in cases occurring in young women age 20–24 years (Buchan & Vessey 1989). This contrasts with falling rates during the same period in both Sweden (Weström 1988) and in America (Rolfs *et al.* 1992). There does not appear to have been a concomitant shift to outpatient diagnosis and treatment of PID in either of these countries. The 40% reduction in hospitalised cases seen in Sweden mirrored a dramatic fall in reported cases of uncomplicated genital tract infections. It is believed that this resulted from an active approach towards prevention, early diagnosis and treatment of chlamydial infections and other sexually transmitted diseases. Educational campaigns directed at both young women and health professionals have led to a raised awareness of the potential risks associated with sexual activity. There has been an increase in demand from both women and doctors for laparoscopy to aid the accurate diagnosis of PID (Weström 1988). Recognition on the part of gynaecologists of the need for identification and treatment of sexual partners has also helped to reduce both new and recurrent cases of PID.

In England and Wales between 1981 and 1990 there was a 37% increase in women attending as new cases to GUM clinics. Gonorrhoea in women halved during this decade, but chlamydial infections continued to rise (Catchpole 1992). Those involved in the care of women can support public health measures aimed at prevention of sexually transmitted diseases by routinely enquiring about sexual behaviour, by screening those women at risk and by arranging for examination and treatment of male partners where appropriate. Physicians working in GUM clinics have long been familiar with these ideas. However, Eynon-Lewis (1988) found that only 39% of general practitioners considered investigations or referral of the male partner in cases of PID. How many gynaecologists in the UK routinely arrange contact tracing after diagnosing PID?

Numerous studies have established the polymicrobial aetiology of PID. Only two prospective studies employing laparoscopy have been reported from centres in the UK (Kinghorn *et al.* 1986; Stacey *et al.* 1992, see p. 992 of this issue). The total number of cases combined is less than 50, but the findings support those of the large Swedish and American studies. In the main, sexually active women with PID either had micro-organisms isolated or serological evidence of pathogens that are recognised to be sexually transmitted, e.g. *Neisseria gonorrhoeae* or *Chlamydia trachomatis*, suggesting a primary role in the acute infection. The role of *Mycoplasma hominis* remains unclear. It is a commensal of the genital tract in sexually active women and has yet to be isolated from the Fallopian tubes in asymptomatic women. Even in cases of PID it is rarely isolated from the Fallopian tubes. Serological evidence suggests that it may be involved in up to 30% of cases of PID (Weström & Mårdh 1990). However, its role may be that of an opportunistic secondary pathogen, invading tissue that has already been compromised by a primary pathogen such as *C.trachomatis*.

The clinical manifestations of upper genital tract infections are in part determined by the characteristics of the invading micro-organism and in part by the hosts' immunological response to the microbial challenge. For any individual pathogen there may be a variable host response. Investigation of women with infertility lends some support to the concept of asymptomatic PID. Serological evidence of *C trachomatis* has been found in up to 70% of women with tubal factor infertility and yet 50% of these women give no history of previous PID (Moore *et al.* 1982). Further elucidation of the immunological mechanisms operating within the female genital tract might help explain the varying presentation and severity of PID and in particular the phenomenon of silent PID.

Clearly any reduction in the incidence of PID would lead to a reduction in the number of women suffering from the associated long term sequelae. Buchan *et al.* (1993 in press) report on morbidity following an initial episode of PID using data from the Oxford Record Linkage study. They confirm that many women become recurrent outpatient attendees with chronic problems, culminating in a high rate of hysterectomy.

Early accurate diagnosis allows instigation of appropriate antimicrobial therapy and this in turn might be expected to improve the clinical outcome. Failure to make a correct diagnosis may lead to late or no treatment with a potential for disease progresion, leading to an increased risk of sequelae. A mistaken diagnosis of PID and inappropriate antimicrobial therapy may delay the diagnosis of other serious intra abdominal pathology. Unfortunately, there is no simple diagnostic algorithm that is both sensitive and specific for PID. The sensitivity of clinical symptoms and signs alone is low when compared with laparoscopy (Jacobson & Weström 1969). Early laparoscopy in conjunction with standardised clinical criteria (Hager *et al.* 1983) has much to recommend it. Diagnostic uncertainty is less likely, the severity of the disease can be assessed and the prognosis for subsequent fertility stated. Although the use of laparoscopy in the diagnosis of PID has increased by 50% in the UK over the period from 1975 to 1985 (Buchan & Vessey 1989), its utilisation is still far from universal.

Antimicrobial regimes must be effective against *N.gonorrhoeae, C.trachomatis* and *M.hominis*, and the facultative aerobic and anaerobic micro-organisms which, although normally commensals of the lower genital tract, can act as secondary invading pathogens in a compromised upper genital tract. Treatment regimes that offer maximum efficacy alongside optimal patient compliance should be used. It is therefore surprising to learn that antichlamydial therapy is still not routinely prescribed to all sexually active women with PID (Eynon-Lewis 1988; Rolfs *et al.* 1992). Currently available antimicrobial agents, although producing clinical and microbiological cures, do not guarantee preservation of tubal function and have not been assessed for their efficacy at preventing long term gynaecological morbidity. Other therapeutic strategies, e.g. adjuvant treatment with non steroidal anti-inflammatory drugs, bed rest versus ambulant therapy and perhaps second look laparoscopy with early adhesiolysis need to be assessed prospectively.

Continuing research is required to improve the specificity of clinical diagnosis, and to determine optimal therapy, but the major challenge is to reduce the incidence of PID. How the targets for reduction of sexually transmitted diseases outlined in the Sexual Health proposals of the Government's recent white paper (HMSO 1992) are to be achieved, and what subsequent effect they will have on the incidence of PID in the UK, remains to be seen.

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OBSTETRICS

The relation between bone mineral density and early pregnancy loss

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ABSTRACT

Objective To determine if women who suffer from early pregnancy loss are at increased risk of osteoporosis later in life.

Design Part of a community screening project for bone mineral density (BMD).

Subjects 392 women aged 50–54 who had had from 0 to 6 miscarriages out of 0 to 8 term pregnancies.

Technique BMD measured using dual energy X-ray absorptiometry at both the lumbar spine and the proximal femur.

Results The mean BMD in nulligravid women was not significantly different from those whose only pregnancies ended in early loss. There was no significant correlation between the BMD at either the lumbar spine or the proximal femur and the number of miscarriages ($r = 0{\cdot}03$ and 0·01, respectively). The BMD of the lumbar spine and femoral neck were not affected by parity ($P = 0{\cdot}08$ and $P = 0{\cdot}87$, respectively).

Conclusion The risk of osteoporosis was not influenced by parity or the number of previous miscarriages.

The human reproduction cycle of pregnancy and lactation applies stress to all physiological systems and the mineral metabolic system, which includes the skeleton, is no exception. During pregnancy, the maternal organism must continuously maintain a normal plasma ionised calcium level in the face of a plasma volume expansion of 1–1·5 litres (Pirani *et al.* 1973) and must transfer 30–35 g of calcium to the fetus by term (Cundy & Kanis 1981). Additionally, the substantial increase in glomerular filtration rate during pregnancy results in increased obligatory urinary calcium losses which are already apparent by 20 weeks gestation (Heaney & Skillman 1971).

A causal relation between pregnancy and generalised osteoporosis has been asserted by some authors (Burrows & Graham 1947; Jackson 1958; Nordin & Roper 1955) but denied by others (Nilsson 1969; Walker *et al.* 1972; Hreshchyshyn *et al.* 1988). In fact, multiparity may have a protective effect against osteoporosis (Goldsmith & Johnston 1975; Stevenson *et al.* 1989). The absence of an overall effect of pregnancy on the skeleton does not, however, preclude the existence of changes in the bone mineral content. Purdie *et al.* (1988) found that the response of the human skeleton to pregnancy is biphasic with an increased bone resorption and consequent lower bone volume in early pregnancy followed by a significant increase in bone volume in late pregnancy. This increase is achieved despite the need to maintain plasma calcium concentration at a time when the plasma volume expansion is maximal and when most of the calcium of the healthy fetus is transferred from the maternal circulation (McCance & Widdowson 1961). Therefore, if the pregnancy terminates in its first half, the woman may be exposed to a deficit in her bone mineral content while being denied the physiological conditions for its restoration.

The condition of osteoporosis is a major clinical problem in western societies and requires significant resources for the care and after care of related fractures (Culliton 1987). Of every 100 women who sustain osteoporotic hip fractures, 20 will be dead within a year and a further 50 will not return to independence in their own homes (Melton & Riggs 1983). The condition thus presents a formidable sociological as well as a clinical problem to our communities and to those responsible for the financial provision of health care. Previous knowledge of risk factors, although extensive, is probably incomplete and there is a need to identify other factors which may be used to target prophylaxis.

Subjects and methods

To examine a possible relation between early pregnancy loss and osteoporosis, 392 white women were recruited in this cross sectional study. All were between 50 and 54 years old and were invited as part of a community bone mineral density screening project in Kingston upon Hull. None suffered from any condition known to affect bone or mineral metabolism. Details of previous pregnancies were obtained including the number of term pregnancies and the number and timing of miscarriages. Women who had had a preterm delivery or miscarriage at less than 10 weeks gestation were excluded.

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Table 1. Numerical distribution of women according to the numbers of miscarriages and the number of term pregnancies.

Term pregnancies (*n*)	Miscarriages (*n*)							
	0	1	2	3	4	5	6	Total
0	24	4	3	0	0	0	0	31
1	23	10	2	1	0	0	2	38
2	68	40	13	6	1	1	0	129
3	48	34	9	2	2	0	0	95
4	22	13	5	1	1	1	0	43
5	12	16	3	3	1	0	0	35
6	7	6	0	1	0	0	0	14
7	2	2	2	0	0	0	0	6
8	1	0	0	0	0	0	0	1
Total	207	125	37	14	5	2	2	392

Table 1 shows the numerical distribution of the women according to their numbers of miscarriages (0–6) and term pregnancies (0–8).

Bone mineral density (BMD, expressed in g/cm^2), was measured in each woman in both the lumbar spine and the right femoral neck using dual energy X-ray absorptiometry (DEXA) (Lunar Radiation Corporation, Madison, Wisconsin, USA). The standard 240 volt AC electricity supply was used to generate power for the X-ray tube to operate at 76 kVp. The tube output is passed through a K-edge filter (350 mg/cm^2 of cerium) to produce two X-ray energies of 38 keV and 70 keV, close to optimal for bone measurements (Mazess *et al.* 1989). The average skin entrance dose of radiation for scanning both the lumbar spine and the femoral neck was <15 uSv. The computer hardware employed in the system was an IBM Personal System/2 Model 70. This analysed the data generated by the scan. The lumbar spine scan was performed with the woman lying supine with her hips flexed by a support block on the scan table in order to promote separation of the spinal vertebrae and reduce lumbar lordosis. The scanning extended from L5–L1 and began, inferiorly, at the level of the anterior superior iliac spines. Results from these vertebrae were taken together to generate a BMD value for the lumbar spine for vertebrae L2–L4, inclusive. Then the support block was removed and the woman's feet were attached to a foot brace. This apparatus allowed the foot of the right leg to be placed in 20° of internal rotation, so bringing the femoral neck into a position at right angles to the scanning head. The scan was made across the upper femoral shaft, the trochanters and the femoral neck. The BMD was measured within an area 6×1·5 cm across the femoral neck.

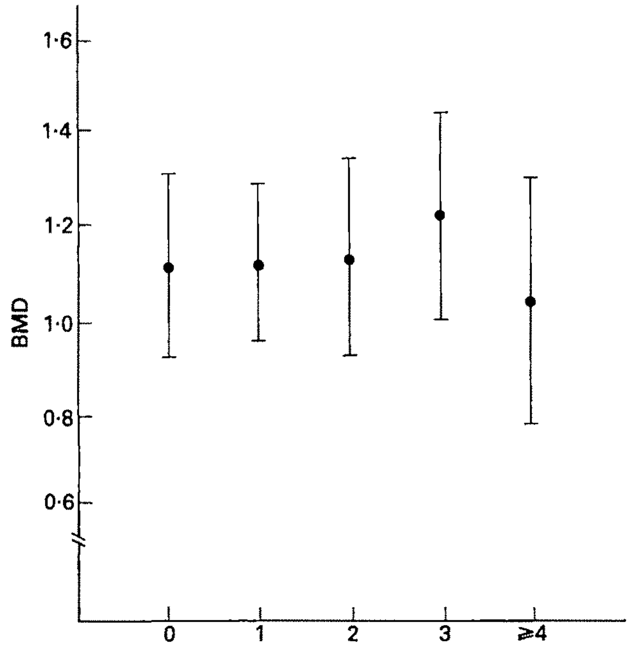

Fig. 1. The relation between the number of miscarriages and the BMD at the lumbar spine (L2–L4); all values as mean±1SD; r = 0·01 (95% CI −0·09–0·11) F—statistics 0 06.

Statistical Analysis

Statistical analysis was performed using EPI Info, Version 5·01 (USD, Incorporated, Stone Mountain, Georgia, USA). The program performs simple and multivariate linear regression according to the methods of Drapers & Smith (1981). It also calculated the means and standard deviations and provided the equivalent of ANOVA and the Student's t test for normally distributed data and the Kruskal–Wallis analysis of variance and the Wilcoxon two–sample test for data not normally distributed.

Results

The median (25th, 75th centile) BMD in nulligravid women (n = 24) was 1·12 (0·95, 1·28) g/cm^2 at the lumbar spine and 0·90 (0·81, 1·04) g/cm^2 at the femoral neck. The median (25th, 75th centile) BMD in the few women who had early pregnancy losses but never achieved term pregnancy (n = 7) was 1·19 (1·00, 1·28) g/cm^2 at the lumbar spine and 0·88 (0·88, 0·96) g/cm^2 at the femoral neck. These results show no statistically significant difference between those two groups (P = 0·64 and P = 0·89, respectively, using Wilcoxon two–sample test).

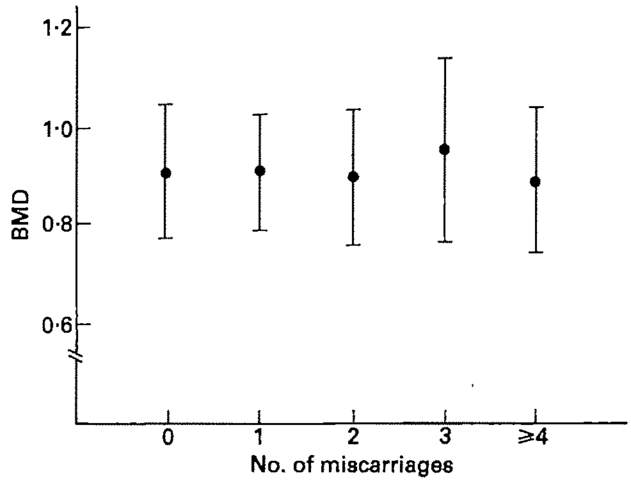

Fig. 2. Relation between the number of miscarriages and the femoral neck BMD; all values as mean±1SD; r = 0·03 (95% CI −0·07–0·13) F—statistic 0·45.

Table 2. The mean and standard deviations (SD) of BMD at the lumbar spine and femoral neck in women with no history of early pregnancy loss.

		Lumbar spine		Femoral neck	
		BMD		BMD	
Term pregnancies (*n*)	Women (*n*)	Mean	SD	Mean	SD
0	24	1·12	0·26	0·93	0·17
1	23	1·22	0·20	0·95	0·15
2	68	1·10	0·16	0·91	0·12
3	48	1·16	0·21	0·91	0·15
≥4	44	1·16	0·18	0·93	0·13

The relation between the number of miscarriages and the BMD at the lumbar spine and the BMD at the femoral neck is shown in Figs 1 and 2, respectively. There was no significant correlation between the number of miscarriages and BMD at either the lumbar spine (linear regression correlation coefficient $r = 0{\cdot}03$) or the femoral neck ($r = 0{\cdot}01$). Because of the small number of women with four or more miscarriages ($n = 9$), the power of the test is low (power = 0·32 to detect a significant difference of 1 SD in BMD). However, if women who had had three or more miscarriages are combined in one group ($n = 23$), the power becomes 0·66. The correlation remains non-significant at either the lumbar spine ($r = 0{\cdot}05$) or the femoral neck ($r = 0{\cdot}02$).

Table 2 shows the distribution of means and standard deviations of BMD at the lumbar spine and femoral neck in women who had never suffered an early pregnancy loss ($n = 207$). This again shows that the BMD at both the lumbar spine and femoral neck was not affected by parity ($P = 0{\cdot}08$ and $P = 0{\cdot}87$, respectively, using ANOVA for multivariate analysis).

Discussion

During the last decade, osteoporosis and its accompanying fractures have reached epidemic proportions. In England alone 37 600 people aged 65 and over sustained a fractured hip in 1985 (Office of Population Censuses and Survey 1987). Any effective strategy for prevention of osteoporosis will require the identification of an at-risk population who may then be offered preventative measures. Established risk factors include increasing age, female sex, white race, premature menopause, prolonged immobility and prolonged use of corticosteroids, while obesity and the use of oestrogen replacement therapy are protective (Kelsey 1989). Bone mineral density accounts for 70–80% of the strength of bone (Mazess 1982) and the risk of fracture increases as the bone mineral density falls (Melton *et al.* 1986; Melton *et al.* 1989; Eriksson & Widhe 1988). Although bone demineralisation has been reported during pregnancy (Purdie *et al.* 1988), the relation between early pregnancy loss and the risk of osteoporosis has not been previously studied.

Our study found that one or several miscarriages did not affect bone mineral density and, therefore, did not increase the risk of osteoporosis. This finding, however, does not contradict the temporary increase in bone resorption in early pregnancy which is reversed physiologically in late pregnancy. Equally, it has been reported that transient osteoporosis during pregnancy is quickly reversed after delivery or termination of pregnancy (Brodell *et al.* 1989). A recently reported case described the virtually immediate resolution of osteoporotic symptoms after termination of pregnancy in a Japanese woman who had developed transient osteoporosis of pregnancy (Chigira *et al.* 1988).

This study supports other studies that deny a causal relationship between parity and osteoporosis (Nilsson 1969; Walker *et al.* 1972; Hreschyshyn *et al.* 1988) but it does not confirm the findings of Goldsmith & Johnston (1975) that parous women with the largest families had the greatest excess of mineral when compared with controls. The difference in results may well be due to the different techniques used; Goldsmith & Johnston used an ^{125}I absorption technique in the distal radius, but we used dual energy X-ray absorptiometry in the lumbar spine and the proximal femur. The latter has a satisfactory precision and, in clinical practice, the DEXA produces a standard deviation of 0·01 g/cm^2 corresponding to a reproducibility of 0·5–1·21% of an average BMD of 1 g/cm^2 (Pacifici *et al.* 1988 & Mazess *et al.* 1989). The stability of the X-ray source eliminates errors related to declining source activity and image resolution is improved (Kelly *et al.* 1988).

Further research is needed to identify the factors which activate and control the shifts in bone mineral content during normal pregnancy. These could have important implications for understanding the pathogenesis of osteoporosis and may yet provide us with a basis for prophylaxis and treatment of this highly prevalent disorder in older women.

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OBSTETRICS

Episiotomy and perineal lesions in spontaneous vaginal deliveries

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ABSTRACT

Objective To evaluate the influence of mediolateral episiotomy on the perineal state after spontaneous, singleton vaginal deliveries with fetus in the occiput anterior position.

Design The study was a population based, observational study. Two approaches were used in the analyses. Initially, we considered the parturients as quasi-randomised to one of three equally sized groups of midwives with different attitudes towards episiotomy. Secondly, we studied the effect of episiotomy on the state of the anal sphincter, controlling for birthweight, parity, and duration of second stage of labour.

Subjects 2188 pregnant women delivering consecutively.

Main outcome measures Perineal lacerations and tear of the anal sphincter.

Results Women allocated to the group of midwives with the lowest rate of episiotomy were more likely to have intact perineum after delivery (OR = 1·8 (1·4–2·2)), had a slight tendency towards more perineal lacerations (OR = 1·3 (1·0–1·5)), but no increase risk of having tear of the anal sphincter, compared with the women allocated to the two groups of midwives with higher frequencies of episiotomy. The second approach showed that episiotomy was related to an increased risk of tear of the anal sphincter (OR = 2·3 (1·2–4·6)). However, this relation was not found among the group of parturients delivered by the midwives with the lowest rate of episiotomy (22%).

Conclusions Our results encourage a conservative approach to the use of mediolateral episiotomy, and in the light of previous findings, it seems reasonable to suggest that episiotomy should ideally be used in about one in five spontaneous vaginal deliveries.

Mediolateral episiotomy has been recommended in the prevention of perineal tears and lesions of the anal sphincter, but the protective effect of episiotomy has never been proven (Thacker & Banta 1983). As women with lesions of the anal sphincter are prone to sequelae several years after delivery (Haadem *et al.* 1988), it is important to examine the relation between episiotomy and perineal tears more closely.

The indications for episiotomy have been related to anatomical factors and medical conditions during labour; however, the large variations in use indicate that other factors, such as national or personal attitudes, may play an important role in the decision about whether or not to carry out episiotomy. Thus, the episiotomy rates range from 14%–96% in primiparas in Great Britain (Sleep *et al.* 1984), while the mean episiotomy frequency of all vaginal deliveries in Belgium is 28% (Buekens *et al.* 1985), in Denmark 56% (Thranov *et al.* 1990) and in the United States 62% (Shiono *et al.* 1990).

We set out to evaluate the effect of episiotomy on the perineal state in a quasi-randomised study of spontaneous deliveries assisted by midwives with different attitudes towards episiotomy.

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Subjects and methods

There were 3737 women delivered in our department between 1 December 1989 and 27 September 1990. Women with singleton pregnancies and spontaneous vaginal deliveries with the head in the occipito anterior position were included in the study. The analysis was further restricted to women delivered by midwives who had 20 or more deliveries during this period. Thus, 2188 women delivered by 43 midwives were included in the analysis.

In Denmark, parturients are assisted by the midwife on duty when they arrive on the labour ward. This allocation can be regarded as a random assignment.

All episiotomies were mediolateral. The midwives were classified into three groups according to the frequency with which they performed episiotomy: (1) Midwives ($n = 14$) with the lowest episiotomy rates and a mean rate of 22% in a total of 807 deliveries; (2) Midwives ($n = 15$) with medium episiotomy rates and a mean rate of 39.8% in a total of 789 deliveries; and (3) Midwives ($n = 14$) with the highest episiotomy rates and a mean rate of 55.7% in a total of 594 deliveries.

Information concerning the use of, and indications for, episiotomy, use of pudendal anaesthesia, duration of second stage of labour, the perineal state after delivery, and birthweight were recorded immediately after labour by the assisting midwife using a specific data recording sheet.

Indications for episiotomy were recorded as either prophylactic episiotomy (rigid perineum or impending perineal tear), or episiotomy for shortening of labour (fetal asphyxia and/or for the relief of the mother or the child). Additional information on maternal age, parity and gestational age at birth was collected from medical records.

Tear of the anal sphincter refers to deliveries where the sphincter has been torn partly or completely. The diagnoses of these lesions were all confirmed by a senior registrar or a consultant.

Data handling & statistics

χ^2-test and the Mantel–Haenszel test for linearity were used for categorical data. Multivariate analysis was performed by logistic regression (Hosmer & Lemeshow 1989; SPSS/PC + Advanced Statistic™ 4·0, 1990). Stratified analysis was carried out as described by Mantel & Haenszel (1959), with tests for homogeneity. For continuous data, means were tested by Student's t-test and ANOVA. Differences were considered statistically significant when the P value was less than 0·05. Odds ratios (OR approximating the relative risk as the events of interest were relatively rare) are presented with 95% confidence intervals (CI).

Results

The distribution of parity, maternal age, birthweight of the newborn, gestational age at birth, and duration of second stage of labour did not differ between the three groups of midwives (Table 1). There was no difference in seniority between the three groups of midwives.

The total number of episiotomies was 815 (37·3%). Figure 1 shows the rate according to each of the 43 midwives classified into prophylactic episiotomy and episiotomy performed for shortening of labour. The rates and indications among midwives with low, medium and high episiotomy rate are shown in Table 2. Both prophylactic episiotomy and episiotomy for shortening of labour were significantly more common among the midwives with higher frequencies of episiotomy than in midwives with low frequencies. However, the relation between these two indications differed between the groups of midwives. In the group with high episiotomy rates, fewer than one in four episiotomies were carried out for shortening of labour, whereas the figures were more than one in three episiotomies in the group of midwives with low episiotomy rates.

Table 2 shows the distribution of perineal tears and frequency of intact perineum according to the three groups of midwives. Women delivered by midwives with low episiotomy rates more often had an intact perineum post-partum (37.5% versus 25.5%, OR for intact perineum = 1·8 (1·4–2·2)). If all deliveries with episiotomy were excluded, there was only a slightly greater incidence of tears in the group of midwives with the lowest proportion of episiotomies, 51.8% versus 45.5% in the two groups with higher rates of episiotomy (OR for perineal tear = 1·3 (1·0–1·5)).

Tear of the anal sphincter was found in 39 (1·8%) deliveries (Table 2). In the group of midwives with low episiotomy rates, lesions of the anal sphincter occurred in 10 (1·2%) women, and in 17 (2·2%) and 12 (2%) women delivered by midwives with medium and high episiotomy rates. However, this difference was not significant.

Lesions of the anal sphincter were found three times more often (CI 1·6–6·0) in parturients with episiotomy than in those without episiotomy. This increased risk remained sig-

Table 1. Background information on 2188 parturients with spontaneous vertex vaginal delivery of singleton children. Classified into three groups according to the frequency of episiotomy used by the assisting 43 midwives.

	Midwives' episiotomy rate			
Variables	Low (*n*)	Medium (*n*)	High (*n*)	*P*
Midwives	14	15	14	
Deliveries	808	783	597	
Episiotomy				
(mean frequency (range))	22·0 (7·2–32·8)%	39·9 (34·2–47·4)%	55·4 (48·5–73·8)%	$P<0·000$
Maternal age				
(mean (SD))	28·3 (4·8) yrs	28·2 (4·7) yrs	28·3 (4·8) yrs	NS
Parity				
(primiparous)	41·5%	45·3%	42·2%	NS
Pudendal anaesthesia				
(mean frequency (range))	40·2 (28·0–67·4)%	44·8 (17·4–76·3)%	46·4 (17·2–81·3)%	NS
% of those with episiotomy	(65·5%)	(63·5%)	(64·3%)	NS
2nd stage of labour				
(mean (SD))	28 (22) min	27 (21) min	27 (22) min	NS
Birth weight				
(mean SD))	3515 (507) g	3507 (508) g	3484 (537) g	NS
Gestational age[a]				
(mean (SD))	282 (12) days	281 (12) days	281 (13) days	NS

[a] Estimated from ultrasound measurement of the biparietal diameter between the 12th and the 21st week of pregnancy and from the menstrual history in cases where no scan was performed.

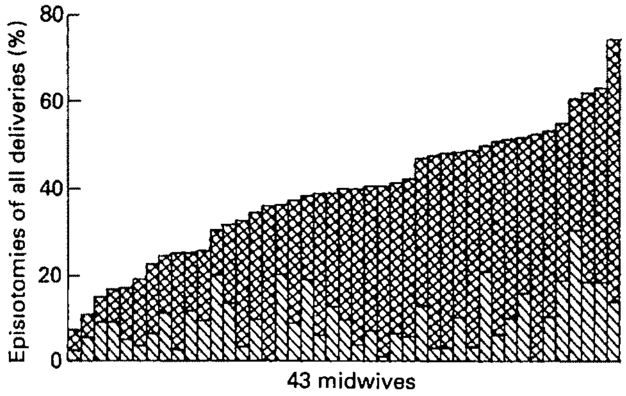

Fig. 1. Rate of episiotomy in each of the 43 midwives classified as all indications (▧) and episiotomies performed for shortening of labour (▩).

nificant (OR = 2·3 (1·2–4·6)) after controlling for parity and weight of the child by stratified analysis (Table 3), and by logistic regression analysis with stepwise variable selection including the variables mentioned and duration of second stage of labour (<30 min/30 min+) (data not shown).

Analyses were carried out after dividing the population of parturients into two groups according to their parity (primiparae/multiparae). These two groups had very similar results to those shown above, although the frequency of episiotomies was higher in primiparous than in multiparous women.

Discussion

The quasi-randomized design implied that the midwives were unaware of the investigation. Thus, they did not change their attitude to use of episiotomy because of awareness of the study. The equal distribution of the baseline characteristics (Table 1), indicates that we achieved random allocation of the parturients to the midwives.

Intact perineum after delivery has previously been shown to be associated with a lower frequency of sequelae than when the perineum has been torn or cut (Kitzinger & Walters 1981; Schultz *et al.* 1990). We found that women delivered by midwives with a low frequency of mediolateral episiotomy overall were more likely to have an intact perineum after delivery, than women delivered by midwives with higher frequencies. This is in agreement with findings from a randomized clinical trial involving 1000 women (Sleep *et al.* 1984). In this study, women with spontaneous vaginal deliveries with fetuses presenting cephalically were randomized to one of two perineal management policies: restrictive use of episiotomy (fetal indication only) or liberal use (prevention of perineal tears as well). We found twice the episiotomy rate (22%) in our group of midwives with the lowest frequency (episiotomy not restricted to fetal indication alone) compared with the rate in the restrictive group (10%) studied by Sleep *et al.* (1984). In spite of this difference in rates of episiotomy, we found fewer women with perineal lesions (52% of deliveries without episiotomy compared with 62%), as well as more women with an intact perineum (37·5% compared with 33·9%) in our low-episiotomy group, although the children in our study were heavier and the distribution of parity the same. These discrepancies, however, could also be due to differences in skill between our three groups of midwives, but the groups were similar with respect to seniority, our best indicator of skill.

The slight tendency towards more perineal tears in the group of midwives with the low rate of episiotomies compared to the groups with higher rates, might give rise to serious speculation if the complications related to lacerations were more severe than those related to episiotomy. However, the frequency of long-term sequelae, such as urinary incontinence and dyspareunia after delivery, has been shown to be independent of whether use of episiotomy has been restricted or liberalised (Sleep & Grant 1987; Thranov *et al.* 1990). Compared with episiotomy, spontaneous lacerations have also been shown to give the same (Harrison *et al.* 1984) or even decreased (Schultz *et al.* 1990) severity of dyspareunia six months after delivery.

Damage to the anal sphincter is the perineal condition giving rise to the most serious long-term sequelae following vaginal delivery. The majority of previous studies concerning the association between episiotomy and lesions of the anal sphincter have dealt with midline episiotomy (Thorp *et al.* 1987; Borgatta *et al.* 1989; Green & Soohoo 1989), which has been shown to be more often related to these lesions than mediolateral episiotomy (Green & Soohoo 1989; Shiono *et*

Table 2. Distribution of perineal lesions and indications for episiotomy in 2188 singleton spontaneous vertex vaginal deliveries. Grouped by frequency of episiotomy of the 43 midwives

	Midwives' episiotomy rate			
	Low *n* (%)	Medium *n* (%)	High *n* (%)	P/P_{trend}
Deliveries	808	783	597	
Indication for episiotomy				
Prophylactic	110 (13·6)	249 (31·5)	251 (42·1)	<0·005/<0·005
Shortening of labour	67 (8·3)	61 (7·8)	77 (12·9)	<0·005/<0·005
State of the perineum				
Episiotomy	177 (22·0)[a]	310 (39·9)[a]	328 (55·4)[a]	
Intact perineum	303 (37·5)	246 (31·5)	152 (25·5)	<0·005/<0·005
Perineal tears	325 (51·8)[b]	220 (47·8)[b]	112 (43·2)[b]	NS/<0·05
Tear of the anal sphincter	10 (1·2)	17 (2·2)	12 (2·0)	NS/NS

[a] Whether episiotomy was carried out or not was unknown in 3, 7 and 5 deliveries in the three groups of midwives, respectively.
[b] Percentage of all women without episiotomy.

al. 1990; Coats *et al.* 1980). We found no decrease in the number of tears of the anal sphincter in the groups of midwives with higher rates of mediolateral episiotomies compared with the low rate group.

Table 3. The relative risk of tear of the anal sphincter in spontaneous vaginal occiput anterior vertex deliveries, stratified according to birthweight, parity and whether episiotomy has been used or not.

Birth weight (g)	Parity	Episiotomy	Tear of the anal sphincter Yes	No	Relative risk (OR)	95% CI
<3000	Primipara	Yes	1	78	0·9	0·3–2·7
		No	1	74		
	Multipara	Yes	0	33	*	*
		No	0	117		
3000–3499	Primipara	Yes	2	192	0·5	0·1–2·7
		No	4	190		
	Multipara	Yes	2	79	6·7	0·8–54·0
		No	1	263		
3500–3999	Primipara	Yes	10	147	4·0	1·0–16·9
		No	2	119		
	Multipara	Yes	3	126	2·2	0·5–9·4
		No	4	362		
4000+	Primipara	Yes	6	67	*	*
		No	0	42		
	Multipara	Yes	1	68	1·3	0·1–14·5
		No	2	176		

The Mantel–Haenszel estimate of the common relative risk (odds ratio) for tear of the anal sphincter following episiotomy, controlled for birth weight and parity was 2·3 (95% CI 1·2–4·6).

*Stratum containing the value 0, thus the relative risk (odds ratio) and confidence intervals (CI) could not be calculated.

Furthermore, our results showed that, after controlling for birthweight, parity, and duration of second stage of labour, the risk of a tear of the anal sphincter was more than doubled following delivery with mediolateral episiotomy compared with delivery without episiotomy.

This result differs from the findings by Shiono *et al.* (1990), who showed that mediolateral episiotomy was associated with a reduced risk in primiparae. However, 46% of the women in their study had forceps deliveries, 16% were not occiput anterior deliveries, and 69% of the women had episiotomy, of which half were midline episiotomies. The criteria for using either of these two methods of episiotomy were not stated in the article, and these factors may explain the difference between their results and our findings.

In contrast to this American study and to our study, Buekens *et al.* (1985) found no association between episiotomy and lesions of the anal sphincter after controlling for birthweight and parity. This study comprised 16 744 spontaneous occipito–anterior vaginal deliveries with 21·9% of the women having had mediolateral episiotomy. The apparently divergent findings related to the association between episiotomy and lesions of the anal sphincter may be explain by the fact that the Belgian study had a relatively low rate of episiotomy (21·9%) which is very close to the mean frequency in our group of midwives with the lowest rate (22%), and much lower than the overall mean frequency in our study (37·3%). When analysing the impact of episiotomy on lesions of the anal sphincter in the particular group of midwives with the low episiotomy rate, and controlling for the same variables as mentioned above, we found no relation between episiotomy and lesions of the anal sphincter (data not shown). This agrees with the findings by Buekens *et al.* (1985).

Accordingly, our results, combined with previous findings, confirm that neither a very liberal approach nor a very restrictive approach (only fetal indication) to the use of mediolateral episiotomy in spontaneous occipito-anterior vaginal deliveries yields optimal results. The ideal episiotomy rate seems to be about 20%, taking into account the condition of the fetus and serious cases of threatened perineal tear. Thus, our results reinforce the recommendations made by Thacker *et al.* (1983) and Sleep *et al.* (1984), who suggest a more conservative approach to the use of episiotomy. According to our findings this approach would result in more women having an intact perineum post partum, a tendency towards slightly more women having spontaneous perineal lacerations, but with no concomitant increase in risk of laceration of the anal sphincter.

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OBSTETRICS

A comparison of perinatal outcome, antenatal and intrapartum care between England and Wales, and France

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ABSTRACT

Objective To compare the national statistics of England and Wales with the national statistics of France, and see if there are significant differences in obstetric care resulting in a significantly different perinatal outcome.
Design Retrospective analysis of national statistics 1970–1989 (latest available figures) relating to perinatal outcome, antenatal and intrapartum care.
Setting HIPE and DoH statistics (England and Wales); INSERM statistics (France).
Subjects Pregnant women residents of England and Wales, and of France.
Interventions Different aspects of obstetric care for which comparable data were available from national statistics.
Main outcome measures Perinatal mortality rate, incidence of low birth weight and preterm delivery; type of antenatal care, number of antenatal visits and in-patient admission rate; induction of labour rate, incidence of acceleration of labour with oxytocin, incidence of spontaneous and operative deliveries and person undertaking delivery; episiotomy rate and postnatal in-patient stay.
Results More antenatal intervention and marginally less intrapartum intervention in England and Wales as compared with France. No significant difference in the perinatal mortality rate, in the incidence of low birth weight or preterm delivery, with similar trends being observed over the two decades.
Conclusion Significant differences in obstetric practices between the two countries without a major difference in perinatal outcome.

Obstetricians agree about the need for providing effective care during pregnancy and childbirth. However, there are wide variations in obstetric practice at regional and national levels as well as over a period of time. Highlighting these differences constitutes a screening test for methods of care requiring evaluation (Enkin *et al.* 1989).

A comparison of obstetric practice of England and Wales with that of France has several advantages. Both countries possess reliable national statistics and use the same definitions of obstetric outcome (perinatal mortality rate, low birth weight, preterm delivery). The population, number of births per annum and life expectancy for women are similar (OMS 1988), (Table 1) and, the training of obstetricians and midwives is similar. It is therefore of immense interest to highlight differences in obstetric care between these populations of similar demographic characteristics and see if they result in a different perinatal outcome.

There are, however, a few limits to this comparison. National statistics are limited by the scarcity of detail about the various procedures and by the different measures of outcome. Obstetric care in England and Wales is mainly confined to the public sector whereas the private sector in France represents 47% of the total number of maternity beds (DoH 1990; Ministere de la Sante 1989) (Table 2). Finally, patients are referred via general practitioners to specialists in England and Wales, whereas patients are self referred in France (Blondel & Schmidt 1984).

Methods

The data are derived from National Statistics, when available, or from surveys on national samples in both countries. For England and Wales, these are mainly HIPE Maternity Statistics (1970–1985) and DoH statistics (after 1985); for France, these are statistics produced by INSERM (French Institute for Health and Medical Research) (1972–1989). The latest available figures have been used.

HIPE statistics are based on a one in ten sample of in-patient records for NHS hospitals. INSERM statistics are based on birth records of all births in ten French regions during 2 separate weeks in 1 year (autumn and spring). In both cases validation checks are performed on the data so that any anomalies present can only represent a tiny part of the material included.

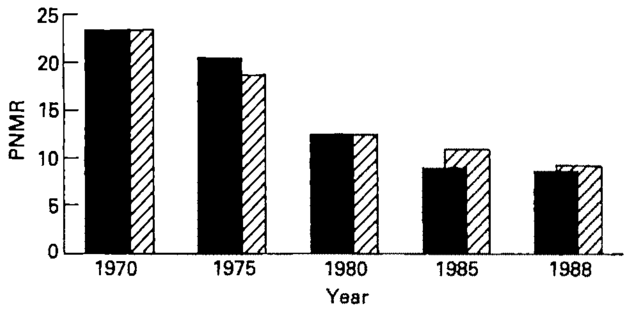

Fig. 1. Perinatal mortality rate. ■ England and Wales; ▨ France.

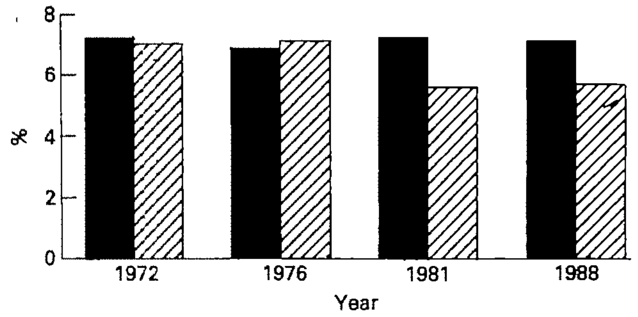

Fig. 2. Low birth weight (<2500 g). ■ England and Wales; ▨ France.

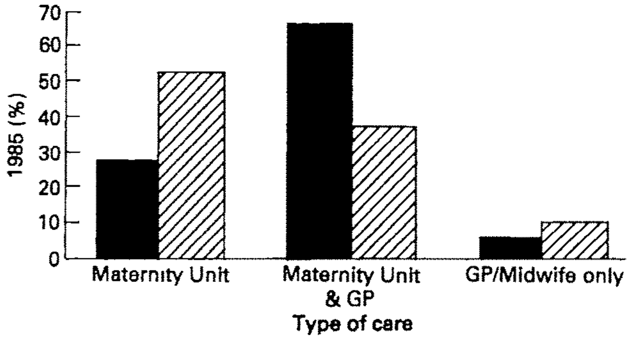

Fig. 3. Type of antenatal care. ■ England and Wales; ▨ France.

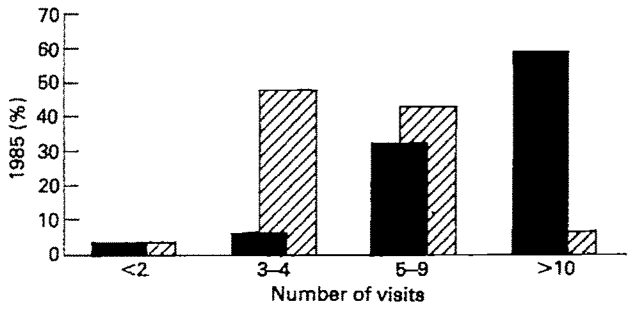

Fig. 4. Number of antenatal visits. ■ England and Wales, ▨ France.

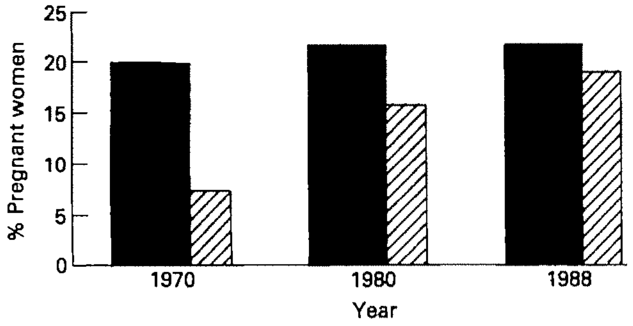

Fig. 5. Inpatient admission during pregnancy. ■ England and Wales, ▨ France

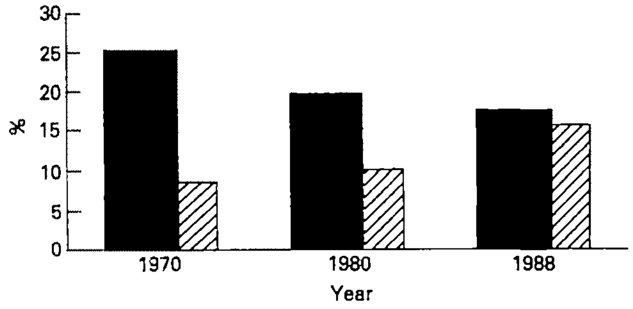

Fig. 6. Induction of labour. ■ England and Wales; ▨ France.

The comparison of the two series, had to be limited to aspects of care for which comparable data were available; in some instances, the British and French information systems did not focus on the same indicators. This phenomenon in itself is informative as it reflects differences in objectives of obstetric care.

Results

Unless otherwise stated all the results refer to the above mentioned references.

Perinatal outcome

There were no major differences in the outcome of pregnancy between the two populations. The crude perinatal mortality rate has shown the same decreasing trend in both countries between 1970 and 1988 (Fig. 1). There were no significant differences in the incidences of low birth weight (Fig. 2) and of preterm births (Kaminsky *et al.* 1986). Furthermore these incidences have not significantly altered in either country between 1970 and 1988. There was no mention of the incidence of pregnancy induced hypertension in either of the countries.

Antenatal care

There was a significant difference in the type of antenatal care. In England and Wales the majority of women received shared care between a GP and a specialist maternity unit, whereas in France the majority of women received specialist care alone (Fig. 3). The total number of antenatal visits also differed. Despite an increase in the number of antenatal visits in France over recent years, this number is still much lower than in England and Wales (Fig. 4). Hospital in-patient admission during pregnancy was also more common in England and Wales than in France, although this proportion is increasing in France (Fig. 5). Finally induction of labour was much more frequent in England and Wales than in France (Fig. 6) In both countries, it was more frequent after 40 weeks. National statistics do not detail the indications for induction.

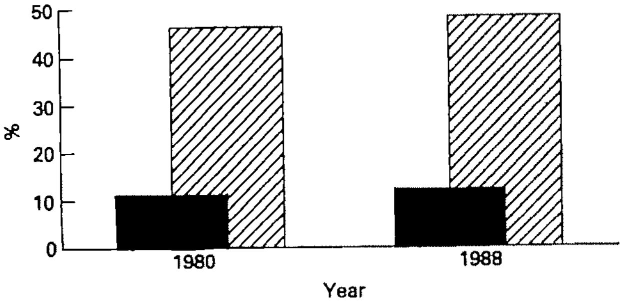

Fig. 7. Acceleration of labour using oxytocin. ■ England and Wales; ▨ France.

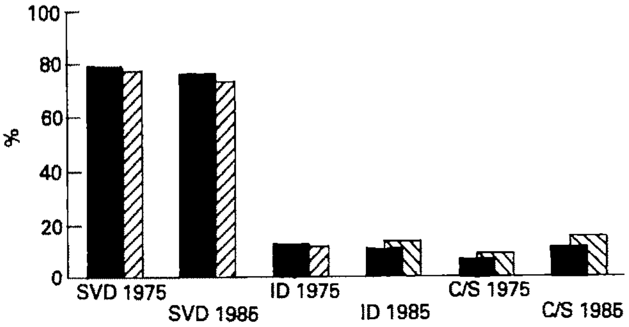

Fig. 8. Mode of delivery. ■ England and Wales; ▨ France.

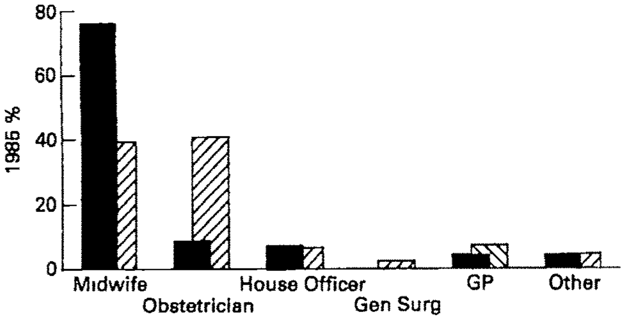

Fig. 9. Person undertaking delivery. ■ England and Wales; ▨ France

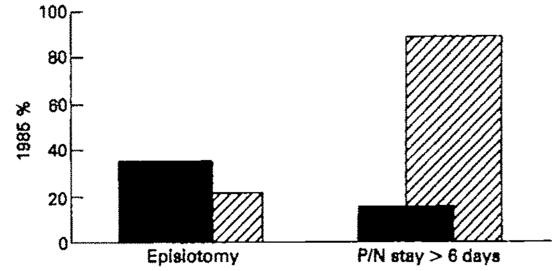

Fig. 10. Episiotomies performed/length of stay. ■ England and Wales; ▨ France

Intrapartum care

Acceleration of labour with oxytocin was, however, much more frequent in France (Fig. 7) and a prolonged first stage was far less common in France (Kaminsky *et al.* 1986). In both countries the frequency of spontaneous vaginal delivery has decreased whilst the frequency of instrumental vaginal delivery and caesarean section has increased (Fig. 8). Instrumental vaginal deliveries as well as caesarean sections were more frequent in France (Fig. 8). Elective caesarean section in particular was more frequent in France (Kaminsky *et al.* 1986). Deliveries were more often conducted by midwives in England and Wales whereas they were more often undertaken by obstetricians in France (Fig. 9). Finally episotomies were more commonly performed in England and Wales, and mothers stayed longer in hospital after delivery in France (Fig. 10).

Discussion

The comparison of the national statistics of England and Wales with those of France has not shown major differences in perinatal outcome between the two countries. Demographic characteristics of pregnant women are very similar in both countries (Kaminsky *et al.* 1986). Many important differences, however, did appear between the obstetric practices as well as in their evolution over time. These differences were too striking to be explained simply by the differences in definitions or quality of data collection.

Table 1. Vital statistics

	England and Wales	France
Population (1988)	47 536 000	56 017 000
No. of births (1988)	657 551	771 268
Life expectancy (women)	77·2	78·5

The different type of antenatal care may be explained by the difference in numbers of specialists as well as by the different patient referral systems (Table 2); women in France are more likely to refer themselves directly to specialists, who are more numerous than in England and Wales.

Differences in the number of antenatal visits may be explained by different recommendations of obstetric manuals and by the legislation of health care. In England and Wales recommendations are one visit per month during the first and second trimesters, one visit every 2 weeks from the 29th to the 36th week and weekly from the 37th week onward (Whitfield 1986). In 1982, the Royal College of Obstetricians and Gynaecologists recommended a smaller number of routine visits (RCOG Working Party Report 1982). In France, recommendations are one visit during the first trimester and one visit per month in the second and third trimester (Merger *et al.* 1979). By law in France, three visits are necessary for pregnant women to be eligible for antenatal allowances, and only four are completely free of charge (Garcia & Saurel-

Table 2. Obstetrics and gynaecology selected statistics

	England and Wales	France
No of obstetric beds (1987)	15 933	30 010
% of deliveries in public sector (1987)	97·8	53·0
No of specialists (1988)	2 724	×2*
No. of midwives (1988)	19 084	×0 5*

*Blondel B. *et al.* (approx)/DoH 1990/Ministere de la Sante (1989)

Cubizolles 1983). No such restrictions exist in England and Wales.

The goals of antenatal care are not the same in both countries. In England and Wales the emphasis is more on the detection of pregnancy induced hypertension and low birth weight; in France, it is more on the prevention of preterm delivery. This is well illustrated by the attitude towards routine vaginal examination which is recommended in France at each antenatal visit in order to assess the cervix, as well as by the French description of the threatened preterm delivery syndrome and risk factor scoring (Merger *et al.* 1979). This may also explain the different rates of hospital in-patient admission during pregnancy.

Induction of labour may be more common in England and Wales for historical reasons (Baird & Thomson 1969), as well as due to the development of efficient techniques of induction. In France more contra indications to induction are described and there is a tendency to caesarean section (Pontonnier *et al.* 1979).

The rate of caesarean section has been increasing in both countries and its justification has been questioned in both (Chalmers & Richards 1977; Barrier & Elhaik 1979). The higher rate in France could be due to their more active management approach and preferences for shorter labour (Kaminsky *et al.* 1986); duration limits have been recommended in France (Merger *et al.* 1979) which are shorter than in England and Wales (Whitfield 1986). In addition, the fact that the majority of French obstetricians practice in the private sector (Ministere de la Sante 1989) means they are more likely to undertake the delivery themselves and assisted deliveries, including caesarean sections, are more common. The different rates of episiotomy may be due to the fact that this procedure was questioned earlier in France than in England and Wales, when an increase in the episiotomy rate was not associated with a decrease in the rate of tears (Rumeau-Rouquette *et al.* 1984).

It is surprising that postnatal stay in France was significantly longer when there is less attention given antenatally and a lower antenatal admission rate. The explanation is not obvious but could be because more French women are covered by private health insurance (Phaff 1986).

Conclusion

The comparison of national statistics has shown no major difference in perinatal outcome despite significant differences in obstetric practice between the two countries. There is therefore a need for better evaluation of obstetric practice before effective care can be achieved. Objective evaluation would best be performed by multicentre prospective randomised controlled trials on methods of management of pregnancy induced hypertension, low birth weight and preterm delivery between the two countries. As long as obstetric care remains based on anecdotal and local experience, one may wonder whether different practices make any difference in outcome to populations of similar socioeconomic status, or is it as in Rugby 'une question de style?'.

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To Sir A. C. Turnbull, KBE, who gave me my first job in this country; to the Birmingham Midland Obstetric and Gynaecological Society who awarded me the registrar prize for presenting this paper in October 1991, and to Mr A. Collingwood, for his endless patience in helping me prepare this paper.

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OBSTETRICS

Perinatal outcome of pregnancies complicated by vaginal bleeding

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ABSTRACT

Objective To examine the effect of first and/or second trimester vaginal bleeding on pregnancy outcome.
Design A prospective one-year birth cohort.
Setting Two northernmost administrative districts of Finland.
Patients 8718 singleton pregnancies, of whom 807 (9·3%) reported bleeding during the first (601) and/or second trimester (206); light bleeding in 595 cases and heavy bleeding in 212. The remaining 7911 women served as a reference group.
Main outcome measures Low birth weight rate (LBW), preterm birth rate, congenital malformations and perinatal mortality rate.
Results Bleeding was most frequent in women of more advanced age (≥35 years old), with previous miscarriages, with infertility problems or using an IUCD prior to the pregnancy. Parity, smoking and social status were not associated with bleeding. Caesarean section rate and placental complications during the third trimester and at delivery were more common among the bleeders than in the reference group. The LBW rate was three-fold among the bleeders and the preterm birth rate two-fold. The risk (OR) of a LBW infant among second trimester bleeders was 4·1 (95% CI 2·6–6·4), that of preterm birth 2·9 (95% CI 1·9–4·6), and that of congenital malformations 2·9 (95% CI 1·7–4·7). No association existed between bleeding and perinatal mortality.
Conclusions Bleeding during the second trimester indicates a poor pregnancy outcome and an increased risk of LBW, and preterm birth and/or congenital malformation.

The frequency of gestational bleeding has been reported to vary from 1% in the material of Funderburk *et al.* (1980) involving 25 387 pregnant women to 22% (Strobino & Pantel-Silverman 1989). Second trimester bleeding in particular has been associated with an unfavourable pregnancy outcome (Funderburk *et al.* 1980; Berkowitz *et al.* 1983), low birth weight (LBW, <2500 grams) (South & Naldrett 1973; Funderburk *et al.* 1980; Berkowitz *et al.* 1983; Batzofin *et al.* 1984; Strobino & Pantel-Silverman 1989), preterm delivery (<37 full weeks) (South & Naldrett 1973; Berkowitz *et al.* 1983) and an increased rate of congenital malformations (South & Naldrett 1973; Ornoy *et al.* 1975; Asanti & Vesanto 1963).

This prospective analysis of 8718 singleton pregnancies is concerned with the perinatal outcome of pregnancies complicated by bleeding during the first and/or second trimester in a geographically defined population with a uniform, high standard of maternity care.

Subjects and methods

The population was a one-year birth cohort (expected date of the delivery between 1 July 1985 and 30 June 1986) collected prospectively from the northern part of Finland in the administrative province of Oulu and Lapland. The deliveries took place in 11 hospitals, comprising one university hospital (38·4% of the cohort), four central hospitals (37·3%) and three regional hospitals (17·4%), each run by specialists in obstetrics and gynaecology, as well as three local hospitals with delivery beds operated by general practitioners (7·0%). All 86 maternity health centres (MHC) in the region participated in the research. The national instructions for antenatal care in Finland (Österlund *et al.* 1978) recommend that every pregnant women should visit a maternal health centre monthly from the beginning of the pregnancy until the 28th week of gestation, twice monthly from 28th to 36th weeks and weekly after that. On average, the women are examined by a general practitioner on three occasions and by a midwife on 12 occasions, including once or twice after the delivery.

The examinations follow a uniform schedule, and women with special risk factors or any signs of pregnancy complications are referred to the maternity outpatient department of the delivery hospital for consultation with a specialist.

The total of 9362 pregnancies resulted in 9478 live and stillbirths, representing 99·0% of all births in the region during

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the period concerned (Sipilä *et al.* 1987). Inadequate data on bleeding were obtained from 529 women. After these cases and those with multiple pregnancies had been excluded, 8718 singleton pregnancies were available for analysis.

The women were enrolled in the cohort during the second trimester (before the 25th week of gestation) during a routine visit to the maternal health centre. All those who had had a miscarriage before the 24th week were excluded. The biological and socio-demographic background factors of the women were obtained from a standardized questionnaire filled in by the women themselves (guided by the midwives) during the routine visit to the maternal health centre in week 24 and during the last visit before delivery or the first visit after delivery. The data concerning the course of the pregnancy were recorded by the midwives and complemented with information collected from the hospital records on complications of pregnancy, delivery, puerperium and the infant. Each of the three questionnaires included a special question concerning bleeding and possible hospitalization on account of it.

The purpose of this study is to investigate the influence of gestational bleeding during the first two trimesters upon the outcome of the pregnancy.

Definitions of terms

Vaginal bleeding was considered light when the women did not need hospital care and heavy when she was admitted to hospital. Smoking refers to smoking by the woman at the end of the second month of the pregnancy. The drinking of alcohol was assessed up to the 24th week of pregnancy with the question 'Have you drunk any alcohol during this pregnancy?' A low birth weight (LBW) infant is one weighing less than 2500 grammes (World Health Organization (WHO) and International Federation of Gynaecology and Obstetrics (FIGO), 1977), and a small for gestational age (SGA) infant refers to babies whose weight is below two standard deviations (<X − 2 SD). Gestational weeks are counted from the last menstrual period.

Statistical analyses

The distribution of background factors in the bleeding groups were compared using conventional χ^2 tests and the incidence of certain perinatal outcomes (LBW, preterm birth, SGA, neonatal ward, congenital malformation, stillbirth and PNM) in these groups are provided in accompanying tables. Corresponding odds ratios (OR) with 95% confidence intervals (CI), adjusted for known biological confounding factors, are reported. A logistic regression model was used for adjustment purposes. The proportions of missing data can be found in the tables.

Table 1. Occurrence of gestational bleeding in singleton pregnancies in the Northern Finland birth cohort 1985–1986

	Light bleeding *n*	Heavy bleeding *n*	Total *n*
First trimester	470	131	601
Second trimester	125[a]	81[b]	206
Total	595	212	807

[a] Including 34 women with light bleeding during both trimesters.
[b] Including eight women with heavy bleeding during both trimesters.

Results

Eight hundred and seven women (9·3%) reported vaginal bleeding during the first or second trimester and were taken to form the study group (Table 1), the other 7911 being used as a reference group.

The differences between the two groups with respect to socio-demographic characteristics, smoking or drinking were not statistically significant (Table 2). Employed women reported more gestational bleeding than housewives ($P<0{\cdot}05$) but the groups did not differ in terms of heavy bleeding, 2·5% versus 2·1%, respectively (P = NS). The occurrence of bleeding seemed not to be influenced by activity at work (sedentary, standing or moving) or strenuousness (physical or mental). Women with a high school education

Table 2. Socio-demographic background factors in single pregnancies with and without bleeding during the two first trimesters.

Background factors	Bleeding *n*=807	(%)	No bleeding *n*=7911	(%)	Total *n*=8718
Marital status					
Married	669	(82·9)	6374	(80·6)	7043
Cohabitant	99	(12·3)	1132	(14·3)	1231
Single	39	(4·8)	404	(5·1)	443
Missing data	0	(0·0)	1		1
Social class[a]					
IV	120	(14·9)	1155	(14·6)	1275
III	425	(52·7)	3939	(49·8)	4364
I–II	125	(15·5)	1252	(15·8)	1377
Farmer	61	(7·6)	633	(8·0)	694
Missing data	76	(9·3)	932	(11·8)	1008
Employment					
Employed	604	(74·8)	5588	(70·6)	6192
Not employed	184	(22·8)	2059	(26·0)	2243
Missing data	19	(2·4)	264	(3·3)	283
Maternal school education					
Compulsory school	174	(21·6)	1849	(23·4)	2023
Trade school	317	(39·3)	3101	(39·2)	3418
Matriculated	228	(28·3)	1961	(24·8)	2189
Missing data	88	(10·8)	1000	(12·6)	1088
Smoking					
Non-smoking	627	(77·7)	6152	(77·8)	6779
<10 cigarettes/day	68	(8·4)	757	(9·6)	825
≥10 cigarettes/day	98	(12·1)	824	(10·4)	922
Missing data	14	(1·7)	178	(2·2)	192
Alcohol drinking					
No	683	(85·4)	6635	(83·9)	7318
Yes	96	(11·9)	920	(11·6)	1016
Missing data	28	(3·5)	356	(4·5)	384
Contraception before pregnancy					
Nothing/barrier	496	(61·5)	5108	(64·6)	5604
Oral contraception	151	(18·7)	1524	(19·3)	1675
IUCD	130	(16·1)	1104	(14·0)	1234
IUCD in situ	15	(1·9)	38	(0·5)	53
Missing data	15	(1·9)	137	(1·7)	152

[a] According to paternal occupation or mother's own if single.

Table 3. Biological background factors and earlier obstetric history in single pregnancies with and without bleeding during the two first trimesters.

Background factors	Bleeding *n*=807	(%)	No bleeding *n*=7911	(%)	Total *n*=8718
Age years					
<19	8	(1·0)	184	(2·3)	192
19–34	671	(83·1)	6712	(84·8)	7383
≥35	128	(15·9)	1015	(12·8)	1143
Parity					
0	262	(32·5)	2681	(33·9)	2943
1–4	511	(63·3)	4770	(60·3)	5281
≥5	34	(4·2)	447	(5·7)	481
Missing	0	(0·0)	13	(0·2)	13
Previous miscarriages					
No	557	(69·0)	6434	(81·5)	6991
1	185	(22·9)	1146	(14·5)	1331
≥2	65	(8·1)	318	(4·0)	383
Missing data	0	(0·0)	13	(0·2)	13
Previous abortions (induced)					
No	689	(85·4)	7081	(89·7)	7770
1	101	(12·5)	738	(9·3)	839
≥2	17	(2·1)	79	(1·0)	96
Missing data	0	(0·0)	13	(0·2)	13
Infertility (examined and/or treated)	61	(7·6)	370	(4·7)	431
No infertility	715	(88·6)	7271	(91·9)	7986
Missing data	31	(3·8)	270	(3·4)	301

(matriculated at least) reported light bleeding more frequently than those with the lowest level of education (7·9% vesus 6·0%; *P*<0·01), but no such difference emerged among heavy bleeders.

Bleeding was significantly more common among those who had used an intrauterine contraceptive device (IUCD) before the pregnancy (Table 2).

The prevalence of gestational bleeding among the youngest women (<19 years) was lower than among the oldest ones (*P*<0·01). Those who bled had had either earlier infertility problems, a previous miscarriage or an induced abortion more often than those in the reference group (*P*<0·0001) (Table 3). No association was found between bleeding and parity, nor with earlier low birth weight, preterm birth or perinatal death.

There was no significant difference between the groups in the mean gestational week on which the first contact was made with the maternal health centre (bleeders 10·5 weeks and the reference group 10·9 weeks), nor in the mean number of visits, but the mean number of consultations at the maternity outpatient department of the delivery hospital was higher for the patients than for the reference group (2·5 SE 2·1 versus 1·4 SE 1·7; *P*<0·001).

Threatened preterm delivery resulted in approximately three times more admissions to hospital for the heavy bleeders than for the reference group (17·0% versus 6·2%; *P*<0·0001).

The caesarean section rate was higher (*P*<0·05) in the cases with bleeding (heavy bleeding 20.3% and light bleeding 15·0%) than in the reference group (13·2%); there was no significant difference in the proportions of elective and emergency sections between the patients and the reference group. Placental complications (i.e. placenta praevia, placental abruption) during the third trimester or at delivery were more common among the bleeders (1·4% versus 0·4%; *P*<0·01).

The frequency of low birth weight was higher in the bleeders (*P*<0·001) and highest of all (11·7%) in women with bleeding in the second trimester. Altogether 18·9% of the preterm births occurred to bleeders, and preterm delivery was almost four times as common in those with second trimester bleeding than in the reference group. Small for gestational age infants were more numerous in the group with bleeding, especially those with second trimester bleeding (Table 4).

The need for observation or care in a neonatal ward was more common among infants born to women who had suffered from bleeding, as were congenital malformations (both *P*<0·001), but no significant association was found between bleeding and either stillbirth or the perinatal mortality rate (PNM <7days) (Table 4).

Logistic regression was used to adjust for bias due to con-

Table 4. Perinatal outcome of single pregnancies without and with bleeding during the two first trimesters of pregnancy.

	Bleeding				Bleeding trimester				No bleeding		
	Light		Heavy		First		Second				
Perinatal outcome	*n*=595	(%)	*n*=212	(%)	*n*=601	(%)	*n*=206	(%)	*n*=7911	(%)	Total
Birthweight <2500 g	43^{a}	(7·2)	14^{a}	(6·6)	33^{a}	(5·5)	24^{a}	(11·7)	182	(2·3)	239
Preterm delivery < 37 weeks	47^{a}	(7·9)	18^{a}	(8·5)	40^{a}	(6·7)	25^{a}	(12·4)	279	(3·5)	344
Small for gestational age ≤2 SD	17	(2·9)	7	(3·3)	14	(2·4)	10	(4·9)	147	(1·9)	171
Admission to neonatal ward	93^{b}	(15·8)	42^{a}	(19·9)	90^{b}	(15·0)	45^{a}	(22·4)	891	(11·4)	1026
Congenital malformation	37^{a}	(6·2)	9	(4·2)	28	(4·6)	18	(9·0)	252	(3·2)	298
Stillbirths	2	(0·3)	0	(0·0)	2	(0·4)	0	(0·0)	32	(0·4)	34
Perinatal mortality < 7 days (including stillbirths)	6	(1·0)	1	(0·5)	6	(1·0)	1	(0·5)	53	(0·7)	60

Significance of difference compared with the non-bleeding group: $^{a}P<0·0001$; $^{b}P<0·01$ (χ^2 for categorical data).

Table 5. Adjusted odds ratios of perinatal outcome for women with light or heavy bleeding and bleeding during first or second trimester of pregnancy.

	Bleeding				Trimester			
	Light		Heavy		First		Second	
Perinatal outcome	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Low birthweight <2500 g	2·9	(2·0–4·0)	2·6	(1·5–4·6)	2·1	(1·5–3·1)	4·1	(2·6–6·4)
Preterm delivery <37 weeks	2·1	(1·5–2·8)	2·3	(1·4–3·8)	1·8	(1·3–2·5)	2·9	(1·9–4·6)
Small for gestational age (⩽2 SD)	1·5	(0·9–2·5)	1·9	(0·9–4·2)	1·3	(0·8–2·2)	2·5	(1·3–4·9)
Congenital malformations (major and minor)	1·9	(1·3–2·8)	1·4	(0·7–2·7)	1·4	(1·0–2·1)	2·9	(1·7–4·7)
Perinatal mortality <7 days	1·4	(0·6–3·4)	0·6	(0·1–4·5)	1·1	(0·4–2·7)	1·3	(0·3–5·4)

founding factors associated with poor perinatal outcome, and odds ratios were adjusted for: previous low birth weight; previous miscarriages; infertility examined and/or treated; contraception method (none or barrier methods/OC/IUCD/IUCD *in situ* at the beginning of actual pregnancy); maternal age (<19 years or ⩾35 years); parity (0-parous or ⩾5-parous); previous preterm birth; and previous stillbirths and/or perinatal mortality (<7 days) (Table 5).

Second trimester bleeding emerged as having the highest OR for low birth weight (OR 4·1; 95% CI 2·6–6·4) and it was also significant ($P<0·01$) for small for gestational age infants (OR 2·5; 95% CI 1·3–4·9). Perinatal mortality appeared not to be associated significantly with bleeding, whereas bleeding during the second trimester rather than the amount of bleeding *per se* tended to be associated with congenital malformations (Table 5).

Discussion

The wide variation in the reported rate of gestational vaginal bleeding among pregnancies ending after the 28th week does not necessarily reflect true biological differences, but is rather a consequence of differences in research design and in the populations studied. Our result is average (9·3%) and differs markedly from the 1% reported by Funderburk *et al.* (1980). The apparent reasons for their very low value are that more than 60% of the women in their series did not have any contact with the health staff before the 21st week of pregnancy and the data were collected retrospectively. The other extreme figure (22·1%) reported by Strobino & Pantel-Silverman (1989), represents a different research design lacking in homogeneity of the series and accuracy of source data.

The lack of association between bleeding and social class is in agreement with the highly comparable Danish series described by Wohlert (1989), but differs from an older Scandinavian investigation (Johannsen 1970); this probably reflects the fact that the impact of social class as a risk factor in general has diminished, at least in Nordic countries (Sipilä *et al.* 1987). Our results confirm the finding of Strobino & Pantel-Silverman (1989) that working during pregnancy slightly increases the risk of bleeding. One explanation may be that working women more often report the bleeding to the health staff in order to qualify for paid sick leave.

The IUCD is a very common contraceptive method in Finland, and about 30% of women of fertile age are fitted with one compared with about 8% in Europe (Kivijärvi 1988). Use of an IUCD before the pregnancy increased the frequency of gestational bleeding, and it may be that mild, silent endometritis could be an explanation for this effect.

Youth has often been considered one of the risk factors for an unfavourable pregnancy outcome (Lee & Corpuz 1988; Scholl *et al.* 1989), although opposite claims have also been made (Gale *et al.* 1989; Sipilä 1988; Walcher & Petru 1989; Wohlert 1989). The present results agree with reports by Strobino *et al.* (1989) and Wohlert (1989) which indicate that youth is not associated with gestational bleeding.

The low birth weight rate among the infants of women with bleeding in pregnancy is two to three times greater than in those without bleeding in all reported series (South & Naldrett 1973; Funderburk *et al.* 1980; Berkowitz *et al.* 1983; Strobino & Pantel-Silverman 1989; Wohlert 1989). The overall prevalence of infants with low birth weights in the Finnish population is 3·9% (National Agency for Welfare and Health 1991), it is also very low by international standards in the present series. Taking this into account, it can be concluded that the relative effect of bleeding in this series is greater than in most of the others (South & Naldrett 1973; Funderburk *et al.* 1980; Berkowitz *et al.* 1983; Batzofin 1984; Wohlert 1989). A special feature of the Finnish antenatal care is the high frequency of check-up visits to a maternal health centre (mean 15) (National Agency of Welfare and Health 1991); early intervention is therefore possible and could contribute to the low percentage of complications in pregnancy and infants with low birth weight (*Br Med J* editorial 1980).

Our investigation failed to show any convincing association between bleeding and congenital malformations, in agreement with other authors (Peckham 1970; Strobino & Pantel-Silverman 1987, 1989). The causal relation between gestational bleeding and malformation in the foetus may, in fact, be bi-directional, but this question only can be solved reliably by means of large prospective surveys with early ultrasound detection of malformation.

Our comparatively unusual observation of no association between bleeding and an increased rate of stillbirths or perinatal mortality is probably not a consequence of the design of the research, although the generally low figures for perinatal mortality in this series interfere with the statistical analysis of possible differences. The fact that Wohlert (1989) reached the same conclusion when studying a comparable population in a similar manner suggests that good general health in the population, environmental factors, free medical care, or all these factors together may contribute to the insignificant effect of gestational bleeding upon perinatal mortality.

The conclusion, as far as implications for antenatal care are concerned, is that the extent and frequency of bleeding are relatively insignificant risk factors but that bleeding during the second trimester calls for special attention in view of an increased risk of low birth weight and preterm birth. These pregnancies should be referred to a delivery hospital with an adequate neonatal intensive care unit.

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OBSTETRICS

A randomised placebo controlled trial of labetalol in the treatment of mild to moderate pregnancy induced hypertension

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ABSTRACT

Objective To determine the need for, and efficacy of, treatment with labetalol in women with mild-to-moderate pregnancy induced hypertension (PIH).

Design Prospective double-blind randomised placebo controlled study.

Setting Maternity units of five hospitals in the Trent Region.

Subjects 144 women (86 primigravid) who developed PIH after 20 weeks gestation.

Interventions Treatment with oral labetalol up to 600 mg daily or placebo with subsequent care of treatment failures in accordance with the attending obstetrician's practice.

Main outcome measures Number of days spent as an antenatal inpatient; the development of proteinuria; the perceived need for induction of labour or elective caesarean section; and gestation age at delivery.

Results Labetalol significantly lowered the blood pressure and reduced the incidence of proteinuria. However, neither the number of days spent as an antenatal inpatient, nor the perceived need for induction of delivery or elective caesarean section, nor the gestation age at delivery differed significantly between the two treatment groups. Post-randomisation consideration of early (≤32 weeks) and late (>32 weeks) onset groups showed the placebo treated early-onset group (n = 15) to have more patients with severe hypertension (>150/110 mmHg) and a greater requrement for additional antihypertensive therapy prior to labour than the group treated with labetalol (n = 16).

Conclusion Anti-hypertensive intervention therapy in pregnancy induced hypertension has been examined using a placebo controlled randomised double-blind trial of labetalol in pregnancy. The maximum blood pressure prior to labour and the incidence of proteinuria was reduced in women on active therapy. However, the length of gestation was not significantly prolonged and indices of clinical outcome were not significantly altered. The appropriateness of pharmacological therapy for late-onset PIH may be questioned.

There is increasing evidence that the cardiac output is not compromised in pregnancy induced hypertension (PIH) or preeclampsia (PE) until fairly late in the clinically apparent disease process (Wallenburg 1990; Macphail *et al.* 1991). It is thus supposed that hypertension is driven by an increase in total systemic resistance. While there is some haemoconcentration, the majority of the increase in systemic resistance is assumed to lie in the peripheral arterioles.

Blockade of the alpha-adrenergic nervous system lowers peripheral resistance; blockade of beta-adrenergic receptors alters baroreflex sensitivity, blocks peripheral adrenoceptors and can reduce cardiac output. Labetalol is a combined alpha- and beta-blocker, the beta-blocking component being slightly selective for the β_2-adrenoceptors of the peripheral and pulmonary vasculature (Brittain & Levy 1976). It has been used for more than a decade in the treatment of hypertension in pregnancy (Riley & Symonds 1982). Over that decade views on the treatment of mild to moderate PIH have shifted. While no one would dispute the need for careful monitoring of such patients, a few of whom will progress to the severe disease, the need for pharmacological treatment of mild and moderate PIH is being questioned. We have therefore undertaken a randomised, double-blind placebo controlled study of the use of labetalol in such women. The primary outcome variable assessed was the birthweight of the infant but other, maternal end points were also examined: the number of days spent as an antenatal inpatient; the development of clinically significant proteinuria; the perceived need for induction of labour or elective caesarean section and the

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duration of gestation. Factors specifically relating to fetal and neonatal outcome from this study have been previously reported (Pickles *et al.* 1989).

Subjects and methods

The risk of having a baby of birthweight less than two SD below the mean (i.e. below the 5th centile) in pregnancies complicated by PIH has been calculated as 2·7 times (Ounsted *et al.* 1985), although her series will have included some women with chronic hypertension since she included those whose blood pressure was ≥140/90 mmHg at any time in pregnancy. In order to detect a halving of the risk, a total of 140 patients would be needed ($\alpha = 0{\cdot}05$, $\beta = 0{\cdot}5$) (Altman 1982). In fact, 152 women with singleton pregnancies were recruited to the trial from five hospitals (Queen's Medical Centre, Nottingham; The City Hospital, Nottingham; King's Mill Hospital, Mansfield; The City Hospital, Derby; and the North Staffordshire Hospital Centre, Stoke-on-Trent) during the 18 month period of the study. Insofar as was logistically possible, all women fulfilling the entry criteria and booked with one of the participating obstetricians were admitted to the study.

Entry criteria were a systolic blood pressure of 140–160 mmHg and a diastolic pressure of 90–105 mmHg after 15 min rest on two occasions 24 h apart, occurring between 20 and 38 weeks gestation and without detectable proteinuria. No woman having a past history of hypertension, renal, metabolic, cardiovascular, respiratory or collagen disease was included. Women were identified in the antenatal clinic and initially admitted for at least 24 h rest and assessment but five patients, from an outlying hospital, were not so admitted.

Allocation to treatment was double-blind and randomized. Labetalol (Trandate®) and identical placebo tablets were supplied by the manufacturers (Duncan Flockhart, Uxbridge, Middlesex) directly to the pharmacies of participating hospitals. Once recruited, allocation to treatment was made by the pharmacies on a random number basis. The codes were not broken until after delivery.

The initial dose was one tablet (100 mg) three times daily. This was increased to a maximum of two tablets three times daily if, in the opinion of the woman's obstetrician, blood pressure control was unsatisfactory. If control was still inadequate, antihypertensive therapy with drugs other than labetalol was initiated, depending on the consultant's current practice.

Recordings of blood pressure were taken at weekly intervals from recruitment until delivery. Patients rested in a semi-recumbent position for at least five minutes before the recording was made. Conventional sphygmomanometers were used, and phase IV Korotkoff sounds were used for the diastolic pressure. Blood pressure data shown in the text are expressed in terms of weeks since entry to the trial.

Proteinuria was assessed (dipstick) every week. Serial serum oestriol (radioimmunoassay) and urate (Technicon SMA 560 Autonalayser, Basingstoke, Hants) measurements were made from women attending QMC and from the majority of patients attending the other centres. Antenatal care after randomization to treatment was given by individual participating consultants according to their current practice.

The study was approved by the ethnics committees of the five hospitals. All patients gave informed verbal consent for inclusion in the study.

Routine ultrasound pregnancy dating was not available in the outlying hospitals. Gestation length was thus assessed for all patients using conventional obstetric criteria. The number of days spent antenatally as an inpatient was recorded for each woman, as was the use of additional antihypertensive agents. The perceived need for labour induction and the method of delivery were recorded. The highest blood pressure recorded during labour was noted, as was the blood pressure during the first postnatal day. The outcome with respect to the babies has been previously reported in detail (Pickles *et al.* 1989).

Data measured on an interval scale and normally-distributed are expressed throughout as the mean value with one standard deviation (SD) in parentheses; 95% confidence intervals (CI) are given for the difference between group means. Other data are expressed as medians with interquartiles in parentheses. Specified group data were compared using the Mann-Whitney test.

Results

Eight of the women recruited initially were subsequently excluded. Four were found not to have fulfilled the entry criteria (one with essential hypertension; two with severe hypertension in the first 24 h; one with proteinuria on admission). Two women withdrew themselves; one developed a rash and was withdrawn and one was mistakenly treated with ward stock labetalol. Thus 144 patients were included in the analysis, of whom 70 were treated with labetalol and 74 with placebo. Table 1 summarizes some basal data for the study population by treatment group. There were no significant differences between the study groups for any of the basal variables.

The administration of labetalol resulted in statistically highly-significant falls in systolic and diastolic pressures at each treatment week by comparison with placebo (ANOVA $P<0{\cdot}0001$ for both). Table 2 shows the systolic and diastolic

Table 1. Some basal characteristics of the study populations at admission to the trial, shown in relation to allocation to treatment. Mean values are shown with the standard deviation in parentheses. There were no statistically significant differences between the two groups

	Labetalol $n = 70$		Placebo $n = 74$	
Characteristics	mean	(SD)	mean	(SD)
Age (years)	25·8	(5·8)	24·7	(4·9)
Primigravidae	40	(57%)	46	(62%)
Gestation age (weeks)	34·0	(2·7)	34·2	(2·6)
Booking: systolic pressure (mmHg)	123·9	(11·2)	126·2	(11·6)
Booking: diastolic pressure (mmHg)	73·1	(7·0)	74·3	(6·4)
Family history of EHT	16	(23%)	14	(19%)
Past history of PIH	16	(23%)	8	(11%)
Smokers	11	(16%)	9	(12%)

Table 2. Blood pressures (mmHg) at various times in the study in patients treated with labetalol or placebo.

	Labetalol n = 70		Placebo n = 74			
Variables	mean	(SD)	mean	(SD)	Difference	95% CI
After 24 h rest	138·7	(9·2)	137·7	(8·3)	−1·0	−1·9 to 1·9
	92·6	(6 4)	93·2	(5·0)	0·6	−1·3 to 2·5
Last before delivery	137·1	(12·5)	142·3	(15·2)	5·2	0·6 to 9·8
	88·9	(10·0)	95·3	(11·6)	6·4	2·8 to 10·0
Maximum in labour	144·0	(12·7)	145·5	(14·0)	1·5	−3 4 to 6·4
	93·8	(8·4)	95 0	(10·2)	1·2	−2·3 to 4·6
24 h post partum	131·2	(12·5)	131·5	(14·5)	0·3	−4·1 to 4·9
	81·9	(10·2)	83 9	(10·9)	2·0	−1·5 to 5·5

pressures after 24 h rest (i.e., on admission to the study), in the week prior to delivery, the maximum recorded in labour and that recorded 24 h after delivery together with the 95% confidence intervals for the difference between group means. The only statistically significant differences in blood pressure between labetalol and placebo-treated patients were those recorded in the week prior to delivery in which they were lower in the patients receiving labetalol. The blood pressure was 150/110 mmHg or less at this time in all except five labetalol-treated patients but exceeded these values in 15 placebo-treated patients to a maximum of 190/120 mmHg. The relative risk of developing severe hypertension in labetalol-treated patients was thus 0·35 (95% CI 0·14–0·92).

Patients receiving labetalol spent a median of 9·5 (6·0–16·0) days as inpatients, very similar to the 11·5 (6·8–17·3) days spent by those taking placebo. Proteinuria was recorded for 31 visits of the 70 women taking labetalol (44%) and at 45 visits of the 74 women receiving placebo (61%). The relative risk of developing proteinuria in the labetalol-treated patients was 0·73 (95% CI 0·53–1·00). Additional antihypertensive agents were given to one woman receiving labetalol and eight taking placebo (P<0·05).

Table 3 shows that there were no statistically significant differences between the treated and untreated groups in gestation age at delivery, onset of labour, mode of delivery or need for additional antihypertensive agents during labour. The blood pressure fell rapidly in the puerperium, (Table 2).

Hypertension arising *de novo* in early third trimester pregnancy is usually regarded as being of more severity than that which arises closer to term (Collins & Wallenburg 1989). A post-randomisation analysis was also performed, considering the patients as either 'early entry' (≤32 weeks) or 'later entry' (>32 weeks). Sixteen women receiving labetalol and fifteen taking placebo were entered early (mean gestation age at entry 29·6 (2·0) and 29·9 (1·8) weeks respectively, compared with 35·2 (1·1) and 35·3 (1·3) weeks for the late entry).

Their booking blood pressures were not significantly different from those entering later. However, the blood pressure recorded prior to delivery was higher in the early entrants, whether treated or not. Thus all five women from the labetalol group who had blood pressures in excess of 150/110 mmHg prior to labour were in the early entry group, together with 10 of the 15 such patients from the placebo group. The values for labetalol were: 147·5 (13·9)/94·4 (12·8) mmHg compared with 134·0 (10·3)/87·3 (8·6) mmHg; 95% CI 7·2 to 19·9 mmHg for systolic and 1·6 to 12·5 mmHg for diastolic pressure; those for placebo-treated patients were: 147·0 (18·9)/100·0 (13·0) mmHg compared with 141·1 (14·1)/94·2 (11·0) mmHg; 95% CI −2·8 to 146 and −0·7 to 12.4 mmHg, respectively. The difference was thus significant in the labetalol-treated group. Seven patients with early onset disease treated with placebo were judged to need additional treatment compared with only one in the labetalol-treated group (P<0·05). Both early onset groups were delivered significantly earlier than the late onset groups; labetalol 35·4 (3·2) compared with 38·5 (1·2) weeks, 95% CI 2·1 to 4·1 weeks; placebo 35·7 (2·9) compared with 38·0 (1·3) weeks, 95% CI interval 1·3 to 3·3 weeks. Treatment was associated with a small prolongation of gestation in the late onset group to 38·5 (1·2) weeks, by comparison with 38·0 (1·3) weeks in the placebo treated group (95% CI −0·1 to 1·0 weeks), but had no significant effect in the early onset groups (35·4 (3·2)) compared with 35·7 (2·9) weeks, respectively. Both early onset groups also had significantly higher rates of elective caesarean section (labetalol 50% and placebo 40%, compared with 11% and 12%, respectively, in the late onset groups; P<0·005, P<0·05 for the treated and untreated groups).

Side effects were noted in eight patients receiving labetalol and in none in the placebo group. Four women complained of

Table 3. Some variables relating to delivery in the two groups of patients· None of the variables differed significantly with respect to treatment.

	Labetalol n = 70		Placebo n = 74	
Variables	mean	(SD)	mean	(SD)
Gestational age at delivery (weeks)	37·8	(2 3)	37·5	(2 0)
Labour				
spontaneous	19	(27%)	18	(24%)
induced	37	(53%)	43	(58%)
caesarean section	14	(20%)	13	(18%)
Delivery				
spontaneous	36	(51%)	32	(43%)
elective section	9	(13%)	4	(5%)
emergency section	8	(11%)	15	(20%)
other	17	(24%)	23	(31%)
Additional antihypertensives in labour	6	(9%)	7	(10%)

headache, three of generalized weakness and one of a rash. None considered the side effects to be of sufficient severity to request withdrawal from the trial.

Discussion

Few would dispute the need for pharmacologic treatment of severe pregnancy-induced hypertension (PIH), either to extend gestational length under close supervision until more favourable fetal maturity is achieved or for the acute lowering of maternal blood pressure prior to delivery. Thus systemic blood pressures of 160/110 mmHg or more in pregnancy will be the subject of active intervention. It is in the 'twilight' area in which pregnancy-induced hypertension as currently defined (Davey & MacGillivray 1986) is present, but has not reached such levels, that uncertainty remains with regard to the need for pharmacological treatment. Since there is no evidence for a biomodal distribution of blood pressure in normo- and hypertensive pregnant women, the imposition of an arbitrary cut-off point for purposes of definition will inevitably include some women who are simply at the high end of the normal range. We have data from 527 Caucasian primigravid women presenting consecutively in Nottingham, of whom 460 were never considered as having pregnancy-induced hypertension. Nevertheless, a systolic blood pressure in excess of 140 mmHg was recorded at least once before labour in 13% of these women, and a diastolic pressure of more than 90 mmHg was recorded in 6·3% (Broughton Pipkin *et al.* unpublished data).

In this randomized, placebo controlled trial of labetalol in mild to moderate PIH we have shown that although labetalol significantly lowers the resting blood pressure and reduces the incidence of severe PIH, the pregnancy outcome in terms of the number of days spent as an antenatal inpatient, gestational age at delivery and the perceived need for early delivery were not affected. These are clinically relevant endpoints with direct implications for the patients and for the maternity services. The fact that there was a significantly greater requirement for additional antihypertensive therapy during gestation in the early onset placebo group shows that labetalol was exerting a clinically satisfactory effect, and yet the outcome variables mentioned did not differ. Other manifestations of the disease evidently influenced the decision to deliver. The demographic characteristics of our study population showed no significant differences between those with early or late onset, or between those subsequently treated with placebo or with labetalol.

Other studies have shown an apparent effect of atenolol and labetalol on the development of proteinuric pregnancy-induced hypertension (Jorge *et al.* 1982; Walker *et al.* 1982; Rubin *et al.* 1983) although this is not a universal finding (Sibai *et al.* 1987; Plouin *et al.* 1988). Recently, a 'typical' odds ratio of 0·72 (95% CI 0·46–1·15) was cited for the effect of β blockers (including labetalol) in PIH/preeclampsia on proteinuria (Collins & Wallenburg 1989). This is very close to that of 0·73 calculated in this study (95% CI 0·53–1·00). It thus seems increasingly likely that the use of labetalol is associated with some diminution in the risk of developing pre-eclampsia.

Most recently it appears that metaanalysis of the trials of low dose aspirin is also showing a reduced incidence of proteinuric pregnancy-induced hypertension (Imperiale & Petrulis 1991). This may suggest that even relatively small decreases in mean arterial pressure are sufficient to protect against a form of pressure induced proteinuria. The proteinuria of preeclampsia is a nonspecific form, presumably secondary to intrarenal vasoconstriction (Wood *et al.* 1976). Its occurrence is indicative of the onset of a more dangerous phase of the disease associated with greater fetal and maternal morbidity and mortality (Page & Christianson 1976), and possibly reflecting microvascular damage in other, less 'visible' tissue beds. Therefore, a treatment which is associated with a lesser degree of protreinuria may be regarded as being of use in ways other than the direct effect on blood pressure.

Our results add to the growing consensus that while mild to moderate pregnancy-induced hypertension must be carefully monitored, preferably in day case units, pharmacological treatment of the disease presenting after 32 weeks gestation does not materially influence outcome and thus may be inappropriate. The condition presenting before this time is more likely to progress to severe PIH and preeclampsia (the majority of such patients in this study were entered early) (Collins & Wallenburg 1989) and it has been fairly written that: '. . . the aim of pharmacologic treatment of moderate hypertensive disease in pregnancy has been to defer or prevent the development of severe hypertensive disease' (Collins & Wallenburg 1989). The somewhat lower incidence of proteinuria during labetalol treatment, together with its efficacy as a hypotensive agent and its lack of demonstrated adverse effects on the fetus or neonate (Macpherson *et al.* 1986; Pickles *et al.* 1989) suggest that it is an appropriate agent to use should antihypertensive therapy be considered necessary.

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OBSTETRICS

Early teenage pregnancies in Hull

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ABSTRACT

Objectives To determine the pattern, obstetric outcome and factors that predispose to pregnancies in young teenagers in Hull.

Design Retrospective study of case records of pregnancies from 1977 to 1988 in girls aged 16 years or less and in a control group of nulliparous women aged 20–24 years.

Setting Hull health district hospitals.

Subjects 1 660 pregnant teenagers and 3 576 nulliparas aged 20–24 years.

Main outcome measures Ages at pregnancy, number of pregnancies per year, gestational age at booking and delivery, antenatal complications, mode of delivery, utilization of contraceptives and some social factors.

Results Of the 1 660 pregnancies in the young adolescents, 59·6% were terminations. The youngest girl was 11. The average annual incidence of early teenage pregnancies was 10·5 per 1 000 girls aged 10–16 compared to 6·4 per 1 000 in England and Wales. Physical characteristics and pattern of antenatal care were similar in the study and control groups. Anaemia was 2·53 times as common in teenagers (95% CI 2·19–2·9; $P<0\cdot0001$) while hypertension alone was 1·7 times as frequent (95% CI 1·28–2·4; $P = 0\cdot002$). Pre-eclampsia and proteinuric disorders were similar in the two groups. Apart from prolonged pregnancy, which was significantly less common in the index group, other gestational ages at delivery and birthweights were the same in both groups. The caesarean section rate in the index group was 0·56 times that in the control group (95% CI 0·4–0·75; $P<0\cdot0001$) but forceps deliveries were 2·37 times as common in the index group (95% CI 1·80–3·12; $P<0\cdot0001$). The uncorrected perinatal mortality rates were 13·6/1000 and 15·7/1000 in the index and control groups respectively.

Conclusion Early teenage pregnancies are common in Hull and, contrary to previous reports, are physically well tolerated by the early adolescents who book early and attend antenatal clinics regularly. Ineffective utilization and ignorance of contraceptive methods are contributory factors. We recommend that emphasis should be placed on providing contraceptive services for teenagers and adopting a more purposeful and holistic approach to sex education.

Adolescent pregnancies are common and deservedly have been given much publicity (Stearn 1963; Utian 1967; Osbourne *et al.* 1981; Bury 1985; Black 1986). This group of women is regarded as high risk because of the pervasive effects of early motherhood on physical and mental health, education, economic independence and social relationships (Black 1986). Several studies have found an increase in various antenatal, intrapartum and postpartum complications. These complications include anaemia, prematurity (Osbourne *et al.* 1981; Simms & Smith 1984), hypertensive disorders of pregnancy (Utian 1967; McIntosh 1984), low birth weight (Duenhoelter *et al.* 1975; Khwaja *et al.* 1986) and a high incidence of operative deliveries. The relative physiological and psychological immaturity of adolescents has been blamed for these complications. Since most of these pregnancies are unplanned, antenatal care has frequently been described as poor (Osbourne *et al.* 1981; Simms & Smith 1984) and not uncommonly absent. Complications are therefore not identified or present late.

In several of the studies cited, various social, environmental, and other confounding variables have been blamed for this trend. In the last three decades, there has been a general improvement in the nutritional status in the United Kingdom. This has been associated with a consistent fall in the age at menarche. Many young girls are therefore much more physically mature than their counterparts two decades ago. In addition, knowledge on contraception is now widely believed to be better. Given these changes, it is expected that there should be a fall in the incidence of adolescent pregnancies and associated complications over the last decade.

Most previous studies have involved small numbers and

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results obtained from them may be difficult to interpret or misleading. In addition, some of these studies have been from areas with a rapidly changing social structure or a large ethnic minority. Hull is an almost homogeneous society whose social structure has altered very slightly since the 1960s. It also appears to have a larger than average proportion of teenage pregnancies. Our objectives were to determine whether there has been a change in the pattern of early teenage pregnancies from 1977 to 1988 inclusive, the pattern of obstetric complications and the factors that may be responsible for these unplanned pregnancies.

Subjects and methods

A manual and computer search of records of legal abortions and deliveries occurring in Hull Health District Hospitals from 1977 to 1988 inclusive was made. Case records of those who were 16 years or less at the time of booking or termination, were retrieved and analysed. The number of early teenage births and legal abortions cared for outside Hull NHS hospitals was obtained from the information department of Hull Health Authority but the case records of these pregnancies were unavailable and they could not be included in the analysis of pregnancy complications and outcome.

The gestational ages at booking (confirmed by ultrasound scan) and at delivery, number of antenatal clinic visits and complications were recorded. Anaemia was defined as a haemoglobin of less than 10·5 g/dl at any stage of pregnancy while a diagnosis of urinary tract infection was based on recorded symptoms and a positive bacteriological culture together or alone. Hypertensive disorders were classified according to the recommendation of Davey (1985). At least one plus of protein in a midstream specimen of urine was regarded as significant, while a blood pressure recording of at least 90 mmHg diastolic and 140 mmHg systolic on at least two occasions was regarded as hypertension. Oedema was not necessary for the diagnosis of pre-eclampsia or eclampsia.

The methods of delivery, duration and complications of labour and birthweights were recorded. Delivery before 37 completed weeks of gestation was classified as preterm while prolonged pregnancy was defined as that progressing beyond 42 weeks. A record of the type of analgesia and use of episiotomies in labour was made. Primary post partum haemorrhage was defined as blood loss of at least 500 mls within the first 24 h of delivery. Fetal outcome was noted and perinatal mortality was defined as any stillbirth after 28 weeks and neonatal death within the first week of life for any delivery after 20 weeks.

All early teenagers who booked for antenatal care in Hull over the study period were assessed by the social worker. Information provided after this assessment was divided into three main categories. These were: (a) unstable families (parents either separated, divorced or mothers unmarried); (b) mothers pregnant as early teenagers; and (c) lack of satisfaction at school (where the teenage stated that she did not like school). Other factors recorded in the patients records that were analysed were use of contraception and smoking habits.

For the purposes of comparison, a control group was selected by JCK using the termination and delivery records at Hull, consisting of all single nulliparous women aged 20–24 who underwent termination, and a selected group of single nulliparas of similar age who had either antenatal and or intrapartum care in Hull District Hospitals. This latter group was matched with the teenagers for social class as determined by the recorded occupation of the parents or next of kin for the early teenagers, and by occupation of husbands or of the women themselves in the case of those in the control group; this group consisted only of women whose deliveries took place immediately before and after that of the index case. Various factors in the index (early teenagers) and control groups were compared using the χ^2 test, t-test with Yates correction or Fisher's exact test, where applicable. Relative risks (RR) and associated confidence intervals (CI) were also calculated. The mid-year population of girls aged 10–16 years (OPCS 1977–1988) and the total number of births and legal abortions, including those who were cared for outside Hull NHS hospitals, was used to calculate incidences.

Results

Over the 12 year period, 54 126 pregnancies were recorded in Hull, 1 660 of which were in early teenagers (aged 16 or less). The annual incidence of early teenage births and legal abortions over this period was 10·5 per 1 000 teenagers aged 10 to 16. 59·6% of the early teenage pregnancies were terminated. One hundred twelve of the early teenage births and legal abortions were managed outside Hull NHS hospitals and are therefore excluded from the comparative analysis below. The pattern of early teenage births and legal abortions over the 12 year period is shown in Table 1. The lowest was in 1982 while the highest was in 1988. Eleven teenagers were aged 11–13 years. 70 aged 14 years, 548 aged 15 years and 919 aged 16 years. The youngest teenager was 11 years.

Over the same period, there were 15 753 pregnancies in single nulligravid women aged 20–24 of which 1 251 (7·9%) were terminated. Of those who received antenatal care, 2 325 met the inclusion criteria and were selected as controls for the 671 teenagers who continued their pregnancies and or

Table 1. Yearly incidences of early teenage pregnancies in Hull.

Year	Births and miscarriages	Legal terminations (total[a] outside NHS)	Total conceptions	Incidence (per 1000)[b]
1977	68	76 (8)	144	11·7
1978	55	70 (10)	125	10 8
1979	39	79 (7)	118	12·4
1980	45	61 (9)	106	9·4
1981	40	85 (6)	125	7·4
1982	36	68 (12)	104	6·3
1983	50	96 (9)	146	9·7
1984	66	83 (10)	149	9 7
1985	72	109 (11)	181	11·8
1986	61	91 (9)	152	10·2
1987	54	92 (11)	146	12·9
1988	85	79 (100)	164	14·3

[a] Includes those whose pregnancies were managed outside Hull NHS hospitals.

[b] Denominator is the mid-year population of girls aged 10–16 years in Hull

Table 2. Antenatal complications (some patients had more than one complication).

Complication	Index group (n = 671) n (%)	Control group (n = 2325) n (%)	Relative risk	95% CI	P
Anaemia	234 (34·9)	321 (13·8)	2·53	2·19 to 2·92	<0·0001
UTI[a]	91 (13·6)	198 (8·5)	1·6	1·26 to 2·01	0·0001
Gestational hypertension	67 (10·0)	137 (5·9)	1·69	1·28 to 2·4	0·0003
Pre-eclampsia	57 (8·5)	184 (7·9)	1·07	0·81 to 1·43	0·68
Proteinuria	58 (8·6)	212 (9·1)	0·95	0·72 to 1·25	0·76
APH[b]	37 (5·5)	111 (4·8)	1·15	0·80 to 1·66	0·50
Miscarriages[c]	14 (2·1)	51 (2·2)	0·95	0·53 to 1·71	0·99
Eclampsia	1 (0·1)	4 (0·2)	0·87	0·02 to 8·77	1·00

[a] UTI = Urinary tract infection.
[b] APH = ante-partum haemorrhage.
[c] These include all deliveries before 28 completed weeks.

delivered in Hull. The descriptive data that follows, refers to the 2 325 controls and the 671 teenagers.

Ninety-two per cent of the early teenagers had never used any form of contraception compared to 19·5% in the control group (RR = 4·7, 95% CI 4·4–5·2, $P<0·0001$). The teenage mothers were 1·29 times as likely to smoke more than 10 cigarettes per day as those in the older group (95% CI 1·18–1·40; $P<0·0001$).

The mean maternal heights measured at booking for antenatal care were 162·73 (SD 4·51 cm) and 163·81 (SD 3·96 cm) in the index and control groups respectively. The mean difference (1·08 cm) was not statistically significant (95% CI 0·95–1·20; P = 0·30). Booking gestational ages were similar in both groups before 25 weeks but 6·9% of the teenage mothers first attended hospital (10 in labour) after 25 weeks compared to 3·2% in the control group (RR = 2·2, P = 0·0001). The pattern of antenatal clinic attendance amongst those booked for such care was similar in both groups, but fewer women in the index group (48·9%) attended antenatal classes than those from the control group (51·7%). This was not statistically significant (RR = 0·95, 95% CI 0·87–1·03; P = 0·20).

Table 2 shows the antenatal complications in both groups. Anaemia, gestational hypertension and urinary tract infections were more common in the early teenagers.

The average weekly weight gain from booking to delivery was 1·35 kgs in the index group and 0·87 kgs in the control group. The mean difference was 0·45 (95% CI 0·23–0·68). The rate of weekly weight gain was respectively 1·45 kg and 1·34 kg in teenagers with and without hypertensive and proteinuric disorders. There was no statistically significant association between excessive weight gain (>0·75 kg/week) and hypertensive and proteinuric disorders (P = 0·4).

The various gestational ages at which delivery occurred are shown in Table 3. Prolonged pregnancy was significantly less common in the index group (RR = 0·5, 95% CI 0·35–0·97; P = 0·03). The pre-term delivery rates were similar in both groups (14·1% versus 15·4%).

Table 4 shows the modes of delivery in both groups. Operative deliveries were collectively similar in both groups (χ^2 = 1·01; P = 0·32) but the caesarean section and forceps rates were respectively lower and higher in the teenagers. The indications for forceps and caesarean deliveries were similar in both groups. Primary post partum haemorrhage was the only intrapartum complication that was significantly more common in the teenagers (RR = 2·2, 95% CI 1·38–3·58; P = 0·009). The epidural rates were 18·7% and 23·4% in the index and control groups respectively. The duration of labour was similar in both groups, the first stage being 7·09 ± 3·85 h and 7·01 ± 4·23 h in index and control groups, respectively; the second and third stages were 38·09 and 6·52 minutes, respectively, in the index group, and 40·48 and 7·2 in the control group.

Table 5 shows the fetal outcome in the two groups. The average birthweights were similar but the perinatal mortality was lower in the index group. As expected, more babies in the index group were adopted or fostered.

The social workers were involved with 77·8% of the 671 teenagers who continued their pregnancies. Social factors identified in this group as possible contributors to the pregnancies included unstable families (63·4%), mothers pregnant at a similar age (12·5%), lack of satisfaction in schools (47·8%) and living in overcrowded homes and high density areas (83·2%).

Discussion

Teenage pregnancy is a major problem in Hull and the United Kingdom as a whole. An estimated incidence of 10·5 pregnancies per 1000 early teenagers is high compared to 6·4 in England and Wales (OPCS Abortion, Birth & Population Statistics 1978–89). Despite this high incidence, we have shown that such pregnancies are not as hazardous as previously thought (Aznar & Bennet, 1961; Claman & Bell 1964; Dott & Fort 1976; Underhill & Aitkins 1978; Khwaja *et al.* 1986). Elliot and Beazley (1980) and Osbourne *et al.* (1981)

Table 3. Gestational age at delivery. P = 0·22

Gestational age (weeks)	Index group n (%)	Control group n (%)
<28	14 (2·1)	51 (2·2)
28–32	25 (3·7)	67 (2·9)
32+–34	13 (1·9)	58 (2·5)
34+–37	43 (5·4)	181 (7·9)
37+–40	278 (41·4)	940 (40·4)
40+–42	288 (42·9)	958 (41·2)
>42	10 (1·5)	70 (3·0)
Total	671	2325

Table 4. Modes of delivery.

Mode of delivery	Index group n (%)	Control group n (%)	Relative risk (RR)	95% CI	P
Spontaneous vertex delivery	529 (78·8)	1872 (80·5)	0·98	0·94–1·02	0·37
Breech vaginal delivery	13 (1·9)	35 (1·5)	1·29	0·68–2·42	0·54
Caesarean section (total)	42 (6·3)	264 (11·3)	0·55	0·40–0·75	0·0001
Elective	9	85			
Emergency	33	179			
Forceps delivery (total)	78 (11·6)	114 (4·9)	2·37	1·80–3·12	<0·0001
Ventouse	1 (0·1)	3 (0·1)	1·15	0·02–14·41	1·00[a]
Miscarriages (excluded)	8 (1·2)	37 (1·6)	0·75	0·35–1·60	0·57
Total	671	2325			

[a] Fisher's exact test.

made similar observations from their reports. While Bury (1985) found that one third of teenage pregnancies are terminated, this is doubled in our series of early teenagers. This is not surprising as the pregnancies are unplanned, unwanted and predominantly in school girls.

The pattern of antenatal care was similar in the early teenagers and the control group although many more young adolescents booked late. This finding differed from that of most other studies (Sarrell & Klerman 1969; Zackler *et al.* 1969; Dwyer 1974; Osbourne *et al.* 1981; McIntosh 1984; Khwaja *et al.* 1986). The absence of any differences in the physical characteristics (heights and weights) at booking in the two groups was again contrary to that of others (Scholl *et al.* 1984; Kelly *et al.* 1985). The differences between our conclusions and those of many others may be due mainly to the above factors. The marked difference in weight gain during pregnancy in both groups is most probably due to the fact that growth is still occurring in the teenagers (Harrison *et al.* 1985).

The most common antenatal complication identified was anaemia. This seems to be the most consistent complication in other studies (Osbourne *et al.* 1981; Scholl *et al.* 1984; Khwaja *et al.* 1986). The anaemia was commonly nutritional as the blood films showed mainly iron deficiency features. We believe that poor dietary habits rather than undernutrition are responsible for this complication. While others (Stearn 1963; Utian 1967; McIntosh 1984) have quoted high incidences of gestational hypertensive and proteinuric disorders in teenagers (often up to 19 years), our findings in these young adolescents were different. The previously reported high incidences may reflect failure to adhere to strict criteria recommended by Davey (1985) for diagnozing these disorders. Because some of these young teenagers are said to find attending clinics and classes with older women difficult and sometimes humiliating (Black, 1986), fright and anxiety may cause raised blood pressures and unless they are repeated after a period of rest and reassurance, false positives are bound to be many. This may be the reason why hypertension alone was more common in our early teenagers who attended antenatal classes less frequently.

Table 5. Birth weights and fetal outcome in both groups. $t = -0{\cdot}60$, $P = 0{\cdot}54$ (for average weight); 95% CI for difference in weights 38–72. SD = standard deviation.

	Index group $n = 663^{a}$ n (%)	Control group $n = 2288^{b}$ n (%)
Birthweight (gms)[c]		
<1000	6 (0·9)	14 (0·6)
1001–1500	12 (1·8)	38 (1·7)
1501–2500	58 (8·8)	125 (5·5)
2501–3000	134 (20·2)	513 (22·4)
3001–4000	419 (63·2)	1426 (62·3)
4001–5103	34 (5·1)	172 (7·5)
Average weight (± SD)	3414 + 644	3431 + 673
Fetal outcome		
Alive (>7 days after delivery)	654	2256
Stillbirths and early neonatal deaths[d]	9	32
Perinatal mortality rate	13·6/1000	15·7/1000
Adopted	66 (10·0)	3 (0·1)
Fostered	7 (1·1)	9 (0·40)

[a] Excludes 8 miscarriages.
[b] Excludes 37 miscarriages.
[c] For all live births after 20 completed weeks of gestation
[d] Deaths occurring within the first week of life.

The outcome of labour was very favourable in the early teenagers with a 78·8% spontaneous delivery rate compared to 80·5% in the older primigravidae. This figure is much higher than that of Osbourne *et al.* (1981). The forceps rate was however more than double that in the control group although the indications were the same. Fright (Stearn 1963) and lack of cooperation in the second stage may account for this difference. When this forceps rate was compared to that from other centres (Osbourne *et al.* 1981), it was much lower. The caesarean section rate of 6·3% was much lower than that in the control group (11·6%) and the hospital average over the 12 year period (10·7%). This is contrary to the findings of Khwaja *et al.* (1986) and suggest that fetopelvic disproportion hitherto thought to be a problem in these young mothers is rare (they did not differ from the older women in the control group in mean stature). Other intrapartum complications were similar in both groups suggesting that these early teenagers physically tolerate labour very well.

The finding of a lower perinatal mortality rate in the teenage group was surprising as most other studies (Utian 1967; Duenhoelter *et al.* 1975; Merritt *et al.* 1980; Khwaja *et al.* 1986) except that of Osbourne *et al.* (1981) found higher rates. Although no obvious explanation could be advanced for this difference, we do however feel that the small numbers of deaths make it difficult to make definite conclusions on perinatal mortality. In this study, we tried to identify some factors that are common to the early teenager at risk of becoming pregnant. Non-contraception (92·2%) was common, 98·7% were attending school at the time of pregnancy and 55% smoked at least 10 cigarettes per day. Most, however, came from the high density, low income council estates. Social factors identified in previous studies (Bury 1985) such as broken homes, unemployed parents, love deprivation at home, school offering very little satisfaction, adopted or fostered and mother pregnant at a similar age were identified in most cases where the social worker was involved.

In conclusion, we have shown that early teenage mothers are not at an increased risk both during pregnancy and labour provided prenatal care is adequate. They appear physically and mentally to tolerate labour very well. A high acceptance of prenatal care is mainly responsible. We believe that this high acceptance in Hull compared to other areas is due to the supportive attitude of parents, relatives and friends.

We have also shown that contraceptive utilization in the early teenagers is inadequate. Although contraceptive services are readily available, this is obviously not synonymous with effective utilization. It is true that these teenage mothers 'do not understand the social reality of under-16 pregnancy and motherhood; do not adequately appreciate the potential of sexual activity; do not realize that biological maturity does not license activating this capacity at will and that once the baby is born, it takes precedence over its mother and at the same time the mother loses her own privileged status as a child' (Coyne 1986).

There is need now more than ever, to reassess the services available to pubertal adolescents. Though we agree with Schaffer *et al.* (1978) that intervention programmes should first identify adolescents at risk of precocious pregnancy and provide them with counselling and birth control services, we strongly feel that such counselling and birth control services should constitute an integral part of the school curriculum manned by district or regional experts who offer the counselling on rotational bases. Since most of these pregnancies are unplanned and unwanted and have severe emotional, physical and educational consequences, access to termination should be easy while efforts are made to encourage prenatal care. Of great importance is the after-care following delivery. This is the period during which families, community midwives, social workers and physicians must be actively involved. Provision for return to education and counselling for postnatal contraception will go a long way to preventing subsequent pregnancies.

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FETAL AND NEONATAL MEDICINE

Erythropoietin levels in amniotic fluid and extraembryonic coelomic fluid in the first trimester of pregnancy

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ABSTRACT

Objective The aim was to measure erythropoietin levels in amniotic fluid and extraembryonic coelomic fluid from 7–12 weeks' gestation.
Subjects Twenty healthy women with ultrasonographically normal first trimester pregnancies prior to surgical termination.
Methods Paired samples of amniotic fluid and extraembryonic coelomic fluid were collected by transvaginal ultrasound guided needling. Erythropoietin was measured in both pregnancy fluids using a radioimmunoassay.
Results There was a highly significant difference between erythropoietin levels in extraembryonic coelomic fluid (median level 15·45 mU/ml; range 6·8–32·1 mU/ml) and those in amniotic fluid (median 5·0 mU/ml; range <5·0–5·8 mU/ml) ($P<0{\cdot}0001$; Mann-Whitney *U*-test). The levels of erythropoietin in maternal serum (median 15·4 mU/ml; range 5·6–29·4 mU/ml) were similar to those in the extra-embryonic coelom ($P = 0{\cdot}81$; Mann-Whitney *U*-test). No relation was demonstrated between erythropoietin levels in amniotic fluid or coelomic fluid and stage of gestation.
Conclusion High levels of erythropoietin in coelomic fluid suggests that the hormone is involved in the process of human extraembryonic erythropoiesis. The exact regulatory role remains unknown.

In the first trimester of pregnancy, erythropoiesis occurs in both extraembryonic and intraembryonic sites (Tavassoli 1991). Yolk sac erythropoiesis begins 15–18 days after conception (Gilmour 1941) and continues up to the 11th week of gestation (Tavassoli 1991). Erythropoietic activity is detectable in the liver and marrow by 6 and 11 weeks of gestation, respectively (Yoffey 1962; Petti *et al.* 1985). The mechanisms regulating embryonic and fetal haemopoiesis are not fully understood. The hormone erythropoietin (EPO) is one of a number of cytokines which may be involved, and is produced mainly by the fetal liver (Finne & Halvorsen 1972). In the fetus, liver and marrow erythropoiesis is regulated by EPO (Zanjani *et al.* 1974; Zanjani *et al.* 1977); yolk sac erythropoiesis may be erythropoietin insensitive (Cole & Paul 1966; Rich & Kubanek 1980).

Transvaginal ultrasonography allows detailed study of embryogenesis and early fetal development. At 7–12 weeks' gestation, the amniotic cavity surrounding the embryo can be clearly distinguished from the extraembryonic coelom which contains the yolk sac. The two sites of erythropoiesis (fetus and yolk sac) are separated by the amnion. Using ultrasound guided needling techniques, samples of fluid can be aspirated from each compartment (Wathen *et al.* 1991). The aim of this study was to measure the levels of EPO in fluid from the amniotic cavity and extraembryonic coelom in early pregnancy.

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Subjects and methods

The study was approved by the District Ethical Committee. Twenty healthy women consented to transvaginal sonography and ultrasound guided amniocentesis prior to surgical termination of pregnancy at 7–12 weeks' gestation. Women with uncertain menstrual data and vaginal bleeding were excluded. Each woman had a normal full blood count. A maternal venous blood sample was taken before induction of anaesthesia. Transvaginal ultrasound was performed using a 5 mHz transducer with a 60 degree viewing angle (Aloka SSD 620, Japan). Gestational age was confirmed by measurement of crown rump length (CRL) and normal fetal heart activity noted in every case. Gestational age was calculated according to the number of completed weeks; a gestational age of 10 weeks included crown rump length measurements of 10 weeks plus 0 days–10 weeks plus six days. A normal secondary yolk sac was seen in the extra-embryonic coelomic cavity of each pregnancy. Transvaginal needle aspiration of the amniotic cavity and the extra-embryonic cavity was performed using the technique described by Wathen *et al.* (1991). Care was taken to avoid traumatising the placenta, fetus, umbilical cord and yolk sac. Paired amniotic and coelomic fluid samples were obtained in each case, and serum and fluids were stored at –20°C until assayed.

EPO levels were measured by radioimmunoassay (Fingerova *et al.* 1991). The detection limit was 5.0 mU/ml and the intra-assay coefficients of variation were less than 10% from 15 mU/ml.

Results

The median values and range of EPO levels were very similar in coelomic fluid and maternal serum ($P = 0.81$; Mann-Whitney *U*-test) (Table 1). These levels were much higher than in amniotic fluid ($P<0{\cdot}0001$ in each case). In amniotic fluid the levels were below the lower limit of detection in 17 of the 20 samples (85%). There was no correlation between EPO levels in the three sites, or between stage of gestation and EPO levels in amniotic fluid, coelomic fluid and maternal serum.

Discussion

This is the first study in which EPO levels have been measured in amniotic fluid and extraembryonic coelomic fluid in early human pregnancy. It is demonstrated that the two fluid compartments have widely different concentrations.

Table 1. Erythropoietin levels in 20 matched samples of amniotic fluid, extraembryonic coelomic fluid and maternal serum at 7–12 weeks' gestation.

Erythropoietin	Amniotic fluid (mU/ml)	Coelomic fluid (mU/ml)	Serum (mU/ml)
Median	5·0	15·45	15·4
Minimum	<5·0	6·8	5·6
Maximum	5·8	32·1	29·4
Interquartile range	5·0–5 0	9·35–19·33	10 2–23·53

Yolk sac haemopoiesis is restricted to erythropoiesis and may be EPO insensitive (Broxmeyer 1991). This could be due to total insensitivity to the action of EPO or to the possibility that yolk sac erythroid cells are maximally stimulated by very small levels of EPO (Tavassoli 1991). The present findings suggest that EPO might be involved in the physiological control of yolk sac haemopoiesis because levels are high in the surrounding coelomic fluid. Animal studies have shown that yolk sac erythroid cells possess EPO receptors (Boussios *et al.* 1989). Yolk sac erythropoiesis declines with gestation but there was no trend in EPO levels in coelomic fluid relative to gestational age.

The exact source of EPO in coelomic fluid is unknown but there are three possible explanations for the high levels of EPO in this site. Firstly, EPO simply may diffuse across the yolk sac membrane. The fetal liver is the main source of EPO (Zanjani *et al.* 1977) and the hormone can reach the yolk sac via the vitelline circulation. Secondly, although maternal EPO does not cross the placenta (Thomas *et al.* 1983), the hormone might reach the coelomic cavity via the decidualised endometrium; it is notable that the levels are very similar in maternal serum and coelomic fluid. Thirdly, immature catabolic mechanisms in the embryonic liver may lead to relatively slow metabolism of EPO (Alpen 1962). Therefore, EPO might accumulate in the coelomic fluid prior to degradation.

The levels of EPO in amniotic fluid are similar to those reported by Zivny *et al.* (1982) in samples collected at 10–16 weeks. In the latter study, all samples at 10 weeks were negative; after 11 weeks samples only showed EPO after concentration. In the present study, EPO was detected in only three amniotic fluid samples: two at 9 weeks' gestation and one at 11 weeks. Even these positive results might have been due to contamination with coelomic fluid. EPO is believed to reach the amniotic fluid in fetal urine, and fetal urine production and micturition do not begin until 11–12 weeks' gestation (Fine & Doubilet 1991).

The biological mechanisms governing extraembryonic haemopoiesis remain unclear. The present findings indicate that EPO may be involved in this process but the exact regulatory role remains unknown.

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FETAL AND NEONATAL MEDICINE

Pulsatile umbilical venous flow and its clinical significance

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ABSTRACT

Objective To determine the prevalence and significance of pulsatile waveforms from the umbilical vein.

Setting A tertiary referral clinic for high risk pregnancies.

Subjects 209 fetuses from 24–41 weeks gestation.

Main outcome measures The presence of pulsatile waveforms in the umbilical vein and the pregnancy outcome.

Results 9/209 fetuses demonstrated pulsatile waveforms and seven had severe growth retardation or congenital anomalies of the heart. Pulsatile flow and abnormalities of the inferior vena cava waveforms were observed in these seven but not in the two infants who were born at term. Double pulsations are described for the first time.

Conclusion Examination of the umbilical venous waveform for pulsatile flow is a useful test as it indicates the presence of asphyxial cardiomyopathy or congenital heart lesions.

Recent advances in Doppler ultrasonic flow velocimetry have increased our knowledge of fetal circulation in normal and pathological states (Stuart *et al.* 1980; Tonge *et al.* 1986; Kirkinen *et al.* 1987). There have been several reports on fetal venous circulation (Chiba *et al.* 1985; Reed *et al.* 1990; Gudmundsson *et al.* 1991; Indik *et al.* 1991). Tsuzaki *et al.* (1990) reported pulsatile flow in the umbilical vein of one fetus with a twin-to-twin transfusion syndrome, and they speculated that this pattern was due to fetal heart failure. However, it has not been confirmed that venous pulsation indicates fetal heart failure.

We examined retrospectively the fetal and neonatal course of fetuses with single or double pulsatile flow in the umbilical vein. We propose that such changes are associated with fetal heart failure from severe hypoxia or congenital heart anomalies.

Subjects and methods

Of 209 fetuses examined by Doppler flow velocimetry between the gestational ages of 24–41 weeks, only nine fetuses demonstrated pulsations in the umbilical vein. When pulsatile flow was recorded in a free loop, the intra-hepatic portion of the vein was next examined in order to exclude the influence of pulsations from the umbilical arteries. All examinations were performed in the absence of fetal breathing movements or other fetal movements; fetal heart rates were within the normal range (120–160 beats per minute) except in case two.

The flow velocity waveforms of these veins were analysed morphologically. Pulsations in the umbilical vein were defined as one or two decrease(s) synchronous with the fetal cardiac cycle (Fig. 1). Further evaluation included flow velocity waveforms from the fetal inferior vena cava which was considered abnormal when there was an absent or reversed flow between two forward flow peaks into the right atrium (Fig. 2).

Results

Pulsatile flow in a free loop of the umbilical vein was seen in nine of the 209 fetuses, but in only seven was it present in the

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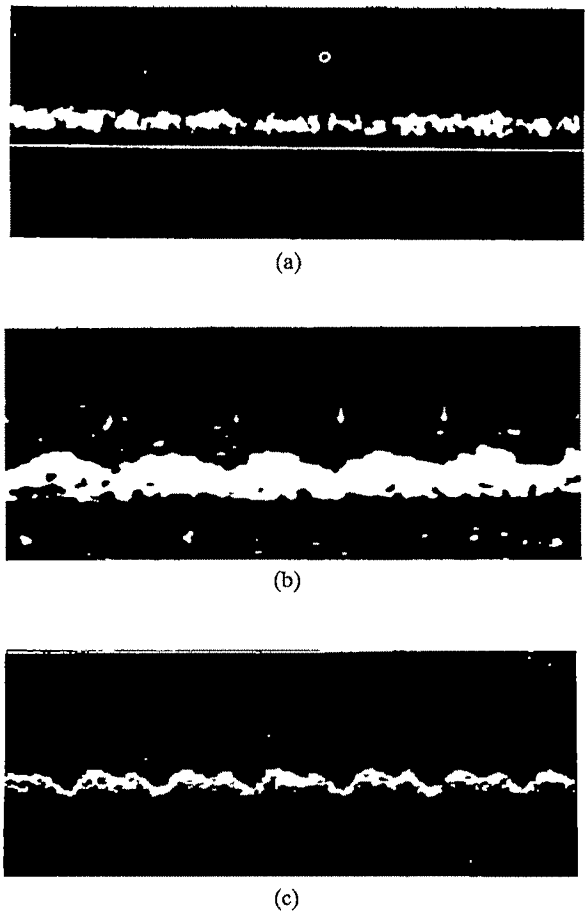


Fig. 1. Flow velocity waveforms in intra-hepatic portion of the umbilical vein: (a) in a normal fetus; (b) the middle panel shows a single pulsation; (c) the lower panel shows double pulsations

intra-hepatic portion of the umbilical vein. Double pulsations were observed in four fetuses (cases 1, 3, 5 and 7) and pulsations were irregular in one case (case 2, Fig. 3). In one (case 7), single pulsations were observed in the 36th week of gestation but these later became double (Fig. 4).

Severe congenital anomalies were present in three fetuses (cases 2, 3 and 7). Four further fetuses had severe growth retardation (below −2·5 SD) and one of them died *in utero* (case 1). The other three were delivered in a hypoxic state and required intensive care, including therapy for heart failure, for more than one week. In these three neonates, it was confirmed by ultrasonography and X-ray obtained soon after birth that both ventricles were greatly enlarged. The enlargement had been demonstrated *in utero* by ultrasonography in one case, but the hearts of the other two could not be observed clearly because of oligohydramnios. In all the fetuses with anomalies or growth retardation, absent or reversed end-diastolic flow was observed in the descending aorta (Fig. 4).

There were no significant complications throughout pregnancy or after birth in the two cases with single pulsations observed only in the free loop of the umbilical vein (cases 4 and 9). These fetuses were born at full term without asphyxia. In these two cases, pulsatile flow was observed only transiently and no significant changes were noted in the flow velocity waveforms of the intra-hepatic portion or the inferior vena cava.

Normal flow velocity waveforms in the inferior vena cava are shown in Fig. 2 (upper). They consist of two forward peak flows into the right atrium with or without one small peak with reversed flow. The two forward peaks are reflections of atrial and ventricular dilatation. A reversed flow reflects atrial contraction but this reversed flow is usually small (Reed *et al.* 1990). When the flow between the first and second forward flow is absent or reversed, we consider it abnormal. This abnormal pattern was observed in all fetuses with anomalies or growth retardation. In case 2, the flow velocity wave pattern in the inferior vena cava was irregular because of fetal arrhythmia (Fig. 3; Table 1, p. 980).

Discussion

There are only a few reports on fetal venous blood flow estimated by Doppler flow velocimetry. It has been noted that umbilical venous flow velocity changes synchronously with fetal breathing movements (Chiba *et al.* 1985; Indik & Reed 1990) otherwise, pulsatile umbilical venous flow is considered to be an ominous sign (Tsuzaki *et al.* 1990; Indik *et al.* 1991). In these reports, however, only single pulsatile flow was described. Double pulsatile flow patterns in the umbilical vein do not appear to have been previously described.

Indik *et al.* (1991) reported single pulsatile flows in the fetuses with growth retardation or anomalies. They also noted that these fetuses had changes in the flow velocity waveforms of the inferior vena cava. Gudmundsson *et al* (1991) also reported pulsatile flows in the umbilical veins and

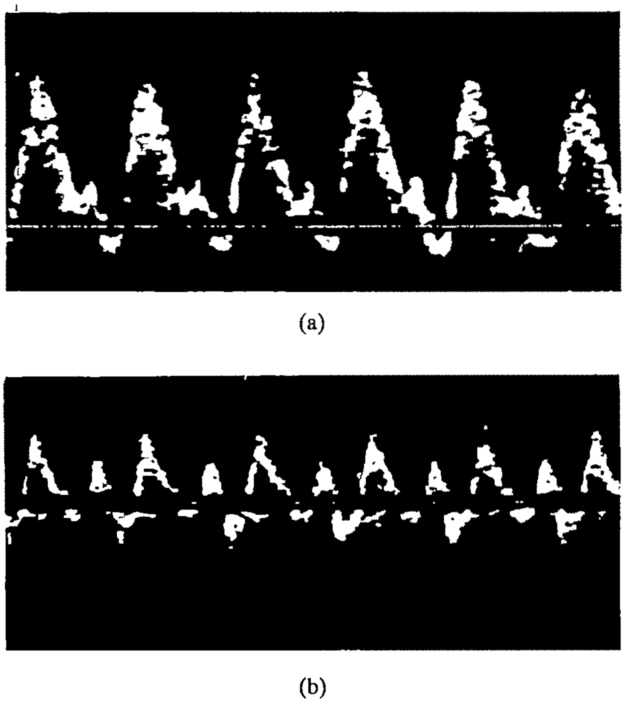
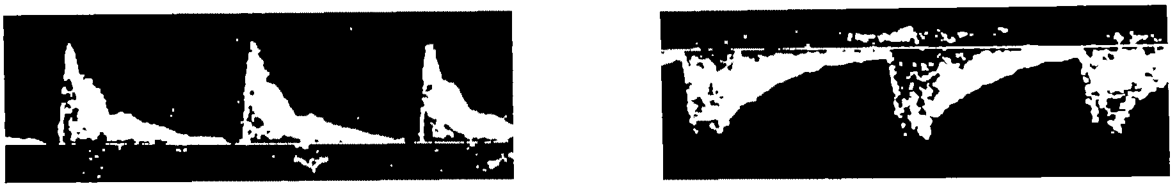
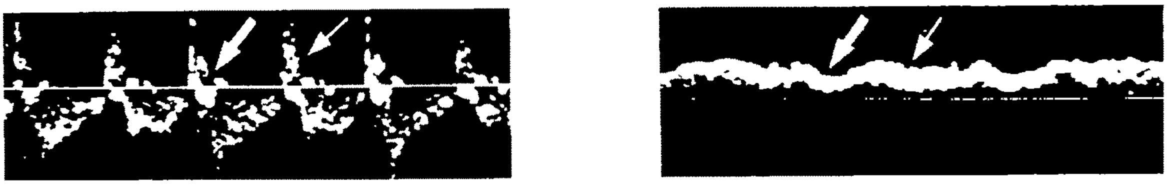


Fig. 2. Flow velocity waveforms in the inferior vena cava (a) in a normal fetus; (b) the lower panel shows an abnormal pattern with the waveform between the two forward peaks being absent or reversed.



Descending aorta

Umbilical artery



Inferior vena cava

Umbilical vein

Fig. 3. Flow velocity waveforms in fetal arrhythmia 2.1 atrio-ventricular block (case 2) In the aorta (upper right), end-diastolic flow was absent. Venous flow changes with ventricular contraction (thick arrow) were larger than without ventricular contraction (narrow arrow). The heart rate from arterial waveforms was half that from venous waveforms.

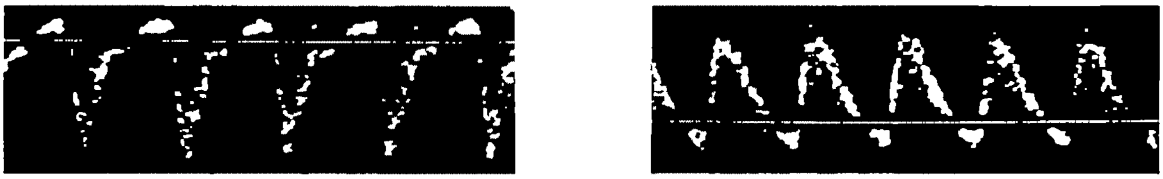
changes in the inferior vena cava blood flow velocity patterns in fetuses with hydrops fetalis. We observed pulsation of the umbilical venous flow in fetuses with growth retardation or anomalies as did Indik *et al.* (1991), but we also observed pulsatile flow in normal fetuses (cases 4 and 9). These pulsations were observed only transiently and only in the free loop of the umbilical vein. All other fetuses with pulsations in the intra-hepatic portion of the umbilical vein had flow changes in the inferior vena cava.

We speculate that pulsations in normal fetuses were due to pulsations of the umbilical arteries. Indik *et al.* (1991) recorded the flow velocity waveforms of the umbilical vein from sites at a distance from the fetal or placental insertions of the cord. It cannot be denied that velocimetry of the umbilical venous flow is affected by arterial pulsations. Therefore, we conclude that umbilical venous flow velocity waveforms should be obtained from the intra-hepatic portion of the umbilical vein.

There have been no reports on double pulsatile patterns These patterns appear closely related to single pulsation, because consecutive changes from single pulsation to double pulsation were observed (case 7). The second pulsation was suspected to be a reflection of the absent or reversed flow velocity between two forward flows into the right atrium in the inferior vena cava in the systolic phase of the cardiac cycle. It is suspected that these phenomena were reflections of increased pressure of the right atrium. This may be due to right heart failure only or tricuspid regurgitation due to right heart failure or atrio-ventricular valve diseases.

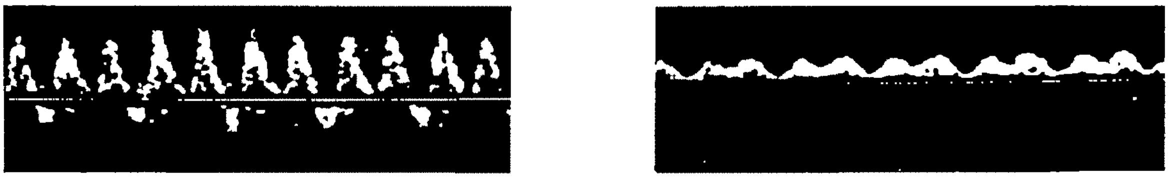
Pulsatile flow in the umbilical vein may suggest fetal right heart failure due to hypoxic myocardiopathy in fetuses with growth retardation. Gudmundsson *et al.* (1991) reported pulsatile flow in the umbilical veins of most fetuses with hydrops fetalis. This finding supports the observation that pulsations in growth retarded fetuses are due to fetal right heart failure.

Pulsations of umbilical venous flow also appeared during



Descending aorta

Umbilical artery



Inferior vena cava

Umbilical vein

Fig 4 Flow velocity waveforms in a fetus with intra-uterine growth retardation with fetal distress (case 7) End-diastolic reversed flow were observed in the aorta and umbilical artery. The waveforms of the inferior vena cava were abnormal, and those of the umbilical vein showed double pulsations.

Table 1. Clinical data of cases of single or double pulsatile flow in the umbilical vein. C/S = caesarean section; NSD = normal spontaneous delivery.

Case	Week of Doppler exam.	Week of delivery	Delivery method	Sex	Birth weight (g)	Apgar score at 1 & 5 min.	Fetal complications
1	24	35	C/S	M	370	0/0	IUFD at 26 week, Twin pregnancy
2	28	38	NSD	F	1391	2/5	IUGR, Trisomy 18, ventricular septal defect, 2:1 Atrio-ventricular block, Hypogenesis of atrio-ventricular valves
3	32	32	C/S[b]	F	1336	1/1	Trisomy 21, Pulmonary stenosis, Common atrio-ventricular valve
4[a]	32	35	C/S	M	1915	8/9	—
5	33	33	C/S[b]	M	1012	1/7	IUGR
6	33	33	C/S[b]	M	1348	6/9	IUGR
7	36	37	C/S[b]	M	1098	4/7	IUGR
8	37	37	C/S[b]	M	2278	1/1	Potter's syndrome
9[a]	38	38	C/S	F	2405	8/9	—

[a] Transient change only

[b] Caesarean section because of fetal distress.

Case 1 was intra-uterine fetal death of one fetus. Another fetus showed no remarkable signs of fetal distress and we observed until the 35th week of gestation, then performed a repeat caesarean section

fetal bradycardia or tachycardia (Indik *et al.* 1991). All the fetuses except case two were examined when the heart rate was within the normal range, and the effect of the heart rate was considered negligible. Ventricular bradycardia was present in case 2, but this fetus also had a valve anomaly making the cause of the pulsations unclear.

In severely asphyxiated neonates the treatment of heart failure due to hypoxia *in utero* is very difficult. It is very important to terminate the pregnancy before fetal heart failure becomes irreversible. The waveforms of fetal blood flow in the umbilical vein or inferior vena cava are quite useful in the evaluation of the fetal heart failure.

Conclusion

We urge estimation of flow velocity waveforms in the intrahepatic portion of the umbilical vein. Pulsatile flows, especially double pulsation patterns, in the umbilical vein indicate fetal heart failure or fetal valve anomalies, if the fetal heart rate is within the normal range. Further examination of the fetus must be done in such cases.

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FETAL AND NEONATAL MEDICINE

Serum prolactin concentration in normal and small for gestational age fetuses

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ABSTRACT

Objectives To study fetal and maternal serum prolactin concentrations in appropriately-grown (AGA) fetuses and in small for gestational age (SGA) fetuses.

Design A cross-sectional study of 27 AGA and 27 SGA fetuses undergoing cordocentesis for prenatal diagnosis or for determination of fetal karyotype and acid-base balance. Serum prolactin concentration was measured by radioimmunoassay.

Setting Harris Birthright Research Centre for Fetal Medicine.

Results In the AGA group, both fetal and maternal serum prolactin concentration increased significantly with gestation ($P<0{\cdot}001$ and $P<0{\cdot}01$, respectively). In the SGA group, the fetal concentration of prolactin was significantly higher ($P<0{\cdot}05$), but the maternal serum prolactin concentration was not different from that of the AGA group.

Conclusions The finding of prolactin in the fetal circulation suggests that the anterior lobe of the pituitary is functioning from at least 12 weeks gestation. The increased serum prolactin concentration in SGA fetuses may be the consequence of hypoglycemic stress on the pituitary or the relative immaturity of the inhibitory hypothalamic–pituitary pathways.

Human prolactin is a member of the polypeptide hormone family which includes growth hormone and placental lactogen (Cooke *et al.* 1981; Wallis 1981). The only generally accepted function of prolactin in the adult human relates to the process of lactation. The hormone has been postulated, however, to have several important functions in the fetus, including lung maturation (Hauth *et al.* 1977; Gluckman *et al.* 1978), osmoregulation (Tyson 1982), and growth of the adrenal gland (Winters *et al.* 1975).

Prolactin has been detected in the pituitary gland of human fetuses from as early as 10 weeks gestation (Aubert *et al.* 1975). Existing data regarding changes in fetal prolactin secretion have been derived from blood samples obtained at termination of pregnancy or from cord blood at birth (Schenker *et al.* 1975, Kaplan *et al.* 1976, Suganuma *et al.* 1986). The results derived from such samples may not necessarily represent physiological levels in the undisturbed fetus; even data derived from elective cesarean section may be influenced by maternal fasting or transient hypotension which could alter placental perfusion and therefore affect the supply of oxygen and nutrients to the fetus (Morriss *et al.* 1974).

The aim of the present study was to investigate the maturation of fetal prolactin secretion in normal pregnancy and to examine possible changes in growth retarded fetuses using blood samples obtained by cordocentesis.

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Subjects and methods

Serum prolactin concentration was measured in 0·2 ml samples, obtained by cordocentesis (Nicolaides *et al.* 1986) at 17–37 weeks of gestation or cardiocentesis at less than 14 weeks gestation from 27 fetuses that were appropriately grown for gestation. The indications for cordocentesis (*n*=25) were: (a) prenatal diagnosis of blood disorders such as hemophilia A (*n*=8); (b) fetal karyotyping for women of advanced maternal age who booked late, those in whom amniocyte culture had failed or those with a low maternal serum alpha fetoprotein suggesting a significant risk of chromosomal defect (*n*=6); (c) karyotyping for fetal malformations such as mild hydronephrosis (*n*=7); and (d) fetal blood grouping in red blood cell isoimmunised pregnancies in which the fetal blood was subsequently found to be Coombs' test negative (*n*=4). In all cases, the fetal abdominal circumference and blood gases at the time of cordocentesis were within our reference ranges for gestation and the fetal karyotype was normal. Furthermore, the fetuses did not have the blood disorder or infection for which they were investigated. In addition, blood was obtained from two fetuses by cardiocentesis immediately before intracardiac injection of potassium chloride for embryo reduction in multi-fetal pregnancies.

Umbilical venous blood was also obtained by cordocentesis at 24–38 weeks' gestation from 27 women referred for fetal karyotyping and blood gas analysis because of ultrasonographic evidence of severe fetal growth retardation (fetal abdominal circumference 2–6 standard deviations below the normal mean for gestation). All mothers were negative for antinuclear factor and showed no serologic evidence of recent toxoplasmosis, rubella, cytomegalovirus, or syphilis infections. The study was cross-sectional, and all fetuses were subsequently determined to be chromosomally normal.

The umbilical venous blood pO_2 and pH were measured by a blood gas analyzer (Radiometer ABL 330, Copenhagen, Denmark) immediately after collection in heparinized syringes. Kleihauer-Betke staining confirmed that all samples contained only fetal blood. The project was approved by the hospital ethics committee and informed consent was obtained from all the mothers.

For measurement of prolactin concentration, fetal and maternal blood (the latter obtained from an antecubital fossa vein immediately before fetal blood sampling) were collected into plain tubes, centrifuged for 10 min at 2000 rpm and the serum collected and stored at –20°C. Prolactin was measured by an immunoradiometric assay incorporating two high affinity monoclonal antibodies (Serono Diagnostics, Slough, UK). The inter- and intra-assay coefficients of variation were 3·4% and 1·6%, respectively.

Statistical analysis

Regression analysis was used to establish the reference range for fetal serum prolactin with gestational age. To determine differences between the maternal and fetal serum prolactin in the SGA and AGA groups, Students *t* test or the Mann Whitney *U* test were used as appropriate. Since fetal prolactin, pO_2 and pH change with gestational age, the individual values of the fetuses were expressed as the number of standard deviations (SDs) by which they differed from the respective normal mean for gestation (delta values) before applying Students *t* test or the Mann-Whitney *U* test.

Results

In the AGA group, both the maternal and fetal serum prolactin concentrations increased linearly with gestation ($r=0{\cdot}525$, $n=27$, $P<0{\cdot}01$; $r=0{\cdot}812$, $n=27$, $P<0{\cdot}0001$, respectively) (Fig. 1). There was no significant association between the fetal and maternal serum prolactin concentrations ($r=0{\cdot}391$), and the mean fetal concentration (1421 mIU/l, range 207–4359) was not significantly different ($t=-0{\cdot}96$, SEM=361·6) from the maternal (1921 mIU/l, range 391–4144).

Most fetal and maternal serum prolactin values were higher than the non-pregnant adult values (mean=165·5 mIU/l, range 53–520) (Fig. 1) established from the study of 68 pre-menopausal patients (Serono Diagnostics, Slough, UK).

In the SGA fetuses, the mean serum prolactin was significantly higher than in the AGA group ($P<0{\cdot}05$), and the mean blood pO_2 and pH were significantly lower ($P<0{\cdot}0001$ and $P<0{\cdot}0001$, respectively) (Fig. 2). The mean maternal serum prolactin concentration (2378 mIU/l, range 1071–5084) was not significantly different from that in the AGA group.

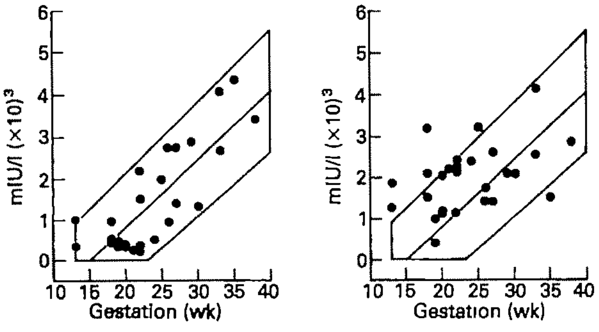

Fig. 1. Individual fetal and maternal serum prolactin concentrations in the normal group plotted on the fetal reference range for gestation (mean, 5th and 95th centiles). The vertical line on the right is the normal range in non-pregnant adults

Discussion

Prolactin is present in the fetal circulation from the first trimester of pregnancy, and the serum concentration, which is not related to that in the mother, is higher than in postnatal life. This finding, together with the demonstration of high circulating levels of thyroid stimulating hormone (Thorpe-Beeston *et al.* 1991), suggests that the anterior lobe of the pituitary is functioning from at least 12 weeks gestation.

The linear increase in fetal serum prolactin concentration with gestation, is consistent with the reported increase in pituitary weight from 10 weeks to term (Kaplan *et al.* 1976), and the demonstration of cytological differentiation and lactotrophs from as early as 12 weeks (Falin 1961; Pasteels *et al.* 1972). However, these findings are in contrast to those of previous studies which examined umbilical cord blood obtained after abortion or birth, and which reported an increase in serum prolactin concentration only after 21–30 weeks gestation (Aubert *et al.* 1975; Kaplan *et al.* 1976; Suganuma *et al.* 1986).

The increase in maternal serum prolactin concentration with advancing gestation is in agreement with the findings of previous studies (Schenker *et al.* 1975; Hercz 1985). This increase may be mediated by oestrogenic stimulation of lactotroph number and function (Aubert *et al.* 1975), and could be aimed at achieving lactation which is the only firmly documented action of prolactin.

In postnatal life, prolactin secretion is thought to be predominantly regulated by an inhibitory dopaminergic system. Thus, dopamine agonist drugs inhibit prolactin secretion and are used in the treatment of hyperprolactinemia. An increase in prolactin secretion is observed during pregnancy and lac-

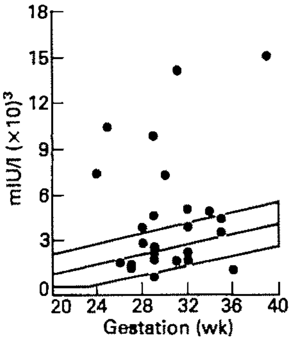

Fig. 2. Individual fetal serum prolactin concentrations in the small-for-gestational age group plotted on the fetal reference range for gestation (mean, 5th and 95th centiles).

tation, but also in renal failure, during episodes of stress or hypoglycaemia, after breast stimulation or following the administration of dopamine antagonists, estrogens, or thyrotropin releasing hormone (Moran-Campbell *et al* 1984).

The findings that fetal and maternal serum prolactin concentrations are higher than in non-pregnant adults may be due to pregnancy-related stimulatory influences that are common to both the fetus and mother, but the lack of significant association between fetal and maternal levels suggests the presence of independent control mechanisms. Experiments in rats have demonstrated that the fetal pituitary has a high sensitivity to prolactin releasing factors, such as thyroid releasing hormone (Khorram *et al.* 1984). In the human fetus, however, it is unlikely that hypothalamic factors play a significant role in regulating prolactin secretion. Thus, Aubert *et al.* (1975) demonstrated that in anencephalic fetuses with no hypothalamus the circulating concentrations of prolactin are normal. Furthermore, several studies involving the administration of drugs to the mother, at timed intervals before delivery and measuring prolactin concentration in umbilical cord blood samples at birth, have demonstrated that fetal prolactin secretion is insensitive to TRH stimulation, and to both dopaminergic and H_2 receptor antagonism (Messinis *et al.* 1982a,b; Robuschi *et al.* 1982; Robuschi *et al.* 1984; Messinis *et al.* 1988; Roti *et al.* 1990).

The increased serum prolactin concentration in SGA fetuses is in agreement with the data of previous postnatal studies (Brimsmead & Liggins 1979; Taketani *et al.* 1984) and may result from increased synthesis or release of prolactin, either due to relative immaturity of the inhibitory hypothalamic–pituitary pathways, or in response to hypoglycemic stress (Woolf *et al.* 1977; Economides & Nicolaides 1989).

Hyperprolactinemia in growth retardation may mediate a series of beneficial adaptations in response to the hostile intrauterine environment of utero-placental insufficiency. Since prolactin stimulates somatomedin-like activity (Hill *et al.* 1977), growth of the fetal adrenal gland (Winters *et al.* 1975), enhances lung maturation (Hauth *et al.* 1977) and has antidiuretic properties (Pullano *et al.* 1989), hyperprolactinemia may represent an attempt to compensate for poor fetal growth, to enhance fetal maturation and to preserve extravascular volume.

Conclusion

Although the precise role of prolactin in intrauterine life remains unclear, the finding of high serum concentration in normal fetuses suggests that it may have an important role in fetal development. The hyperprolactinemia of growth-retarded fetuses could be considered as a response to a hostile intrauterine environment with possible beneficial effects.

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FETAL AND NEONATAL MEDICINE

Alpha thalassaemia hydrops fetalis in the UK: the importance of screening pregnant women of Chinese, other South East Asian and Mediterranean extraction for alpha thalassaemia trait

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ABSTRACT

Objective Alpha zero (α^0 or α-1) thalassaemia is an important genetic risk for women originating from Hong Kong, Singapore, Vietnam, Thailand, the Philippines or South China. Cypriots are also at risk. Carriers of α^0 thalassaemia trait can be detected by routine haemoglobinopathy screening. When a couple are both carriers, in each pregnancy there is a 25% risk that the fetus will have α thalassaemia hydrops fetalis; this is fatal for the fetus and carries serious obstetric and psychological risks for the mother. Most informed couples at risk request prenatal diagnosis and selective abortion. This study investigates the effectiveness of screening, counselling and prenatal diagnosis for α thalassaemia hydrops fetalis in the UK.

Design Retrospective analysis of the notes.

Subjects 18 couples attending University College Hospital London for prenatal diagnosis of α thalassaemia hydrops fetalis since 1982.

Results The study shows underdiagnosis of both α^0 thalassaemia trait and α thalassaemia hydrops fetalis leading to avoidable stillbirths and complications in pregnancy.

Conclusion We recommend early screening for α^0 thalassaemia trait for all women of Southeast Asian or eastern Mediterranean origin and the offer of prenatal diagnosis when indicated. The diagnosis of α thalassaemia hydrops fetalis should be considered in women of the relevant ethnic origin who have a stillbirth, neonatal death, abnormal ultrasound findings at fetal anomaly scanning (especially a large placenta), or who develop pre-eclampsia.

It is standard antenatal practice to screen women ‘not of northern European origin’ for haemoglobin disorders (British Society for Haematology 1988). The objective is to identify and inform carriers, and invite their partner for testing. Couples of carriers may have a one in four risk of a homozygous (affected) child in each pregnancy. They require genetic counselling and the offer of prenatal diagnosis (PND) when appropriate.

Fetal haemoglobin (Hb F) consists of two alpha (α) chains and two gamma (γ) chains. Adult haemoglobin (Hb A) consists of two alpha chains and two beta (β) chains. The common major haemoglobin disorders (β-thalassaemia and sickle cell disease) involve the β chain and so do not affect the fetus. By contrast, because α-chains are present in both fetal and adult haemoglobin, severe alpha chain disorders can cause fetal pathology and may create risks for the mother.

There are two main forms of α-thalassaemia (Higgs *et al.* 1989). α-chain synthesis is directed by two alpha genes arranged in tandem on chromosome 16 (so everyone has four α genes). Alpha plus (α^+ or α-2) thalassaemia trait, in which one alpha gene on one chromosome is deleted, is almost always harmless. It is very common in both the heterozygous and homozygous state among people of African, Afro-Caribbean, south Asian (Indian, Pakistani, Bangladeshi) and eastern Mediterranean extraction (WHO 1990). In heterozygotes, haemoglobin synthesis is slightly reduced, causing only a moderate reduction in red cell size (mean cell haemoglobin (MCH), approximately 24–30 pg; normal range 28–32 pg). In homozygotes, red cell changes are more marked, the blood picture resembling that of β thalassaemia trait (MCH approximately 19–24 pg) but with a reduced or normal Hb A_2 level. There is no associated pathology.

For practical purposes, genetic risk is limited to the more severe alpha zero (α^0 of α-1) thalassaemia trait, in which both alpha genes are deleted from the same chromosome leading to a 50% reduction in haemoglobin synthesis in heterozygotes and severe pathology in homozygotes. Alpha zero thalassaemia trait is found predominantly in people of Southeast Asian (Chinese, Thai, Vietnamese, Malaysian, Philippino), eastern Mediterranean (Greek and Turkish Cypriot, Greek) and occasionally of Middle Eastern origin. There is marked microcytosis as in β-thalassaemia trait, but the Hb A_2 is low or normal. Hb Barts (consisting of unpaired γ chains) is present in the cord blood at birth, and Hb H bodies (consisting of unpaired beta chains) are usually detectable on careful examination of the blood film of carrier adults. Among Southern Chinese 5–6% carry α^0 thalassaemia trait (Zhang *et al.* 1986; Petrou *et al.* in preparation); therefore, when a Chinese carrier is pregnant there is a 5–6% chance of the partner also being a carrier, and a 1–1·5% chance of giving birth to a hydropic baby. Carrier testing of the partner is essential to confirm or exclude this risk.

In homozygous fetuses there is no normal alpha globin chain synthesis, and no Hb F can be made; the blood contains only the abnormal haemoglobin Barts and a small amount of Hb Portland which consists of primitive embryonic zeta and epsilon globin chains. The resulting severe fetal anaemia leads to asphyxia, hydrops fetalis, and stillbirth or neonatal death. Homozygous α^0 thalassaemia can be diagnosed definitively prenatally in the first trimester of pregnancy by DNA methods. In the second trimester stillborn baby it can be diagnosed by cord blood electrophoresis and/or globin biosynthesis studies.

Fetal death can occur at any stage of gestation from about 26 weeks to term. Liveborn infants die in the first few minutes, mainly because of pulmonary hypoplasia. Common maternal complications are pre-eclampsia and eclampsia, pre- or post-partum haemorrhage, and obstructed delivery due to the grossly distended fetal abdomen requiring caesarean section or even embryotomy (Liang *et al.* 1985; WHO 1990). At delivery gross hydrops and compression often cause an abnormal appearance with short limbs and facial distortion and can lead to a misdiagnosis of 'multiple congenital anomalies'. Internal congenital abnormalities (such as ventricular septal defect or atrial septal defect) related to the early onset of anaemia *in utero* are common (Liang *et al.* 1985). The placenta is large, weighing about 1 kg at delivery. Since the diagnosis is not immediately obvious, α-thalassaemia hydrops fetalis should be suspected in any stillbirth or neonatal death, with or without congenital abnormalities, if the mother is of Chinese or other Southeast Asian, or Cypriot extraction. Cord blood should be sent for haemoglobin electrophoresis.

Couples at risk for a fetus with α-thalassaemia hydrops fetalis can be identified prospectively (i.e., before they have given birth to an affected child) by routine haemoglobinopathy screening. This involves Hb electrophoresis and measurement of the red cell indices (British Society for Haematology 1988). A mean cell haemoglobin of less than 27 pg and/or a mean cell volume (MCV) of less than 76 fl suggest thalassaemia trait. To distinguish alpha from beta thalassaemia trait, the Hb A_2 level is measured: a value of more than 3·5% is diagnostic of β thalassaemia trait. However, microcytosis with a normal or low Hb A_2 level is common. It can indicate iron deficiency or an unusual type of β thalassaemia trait, but is often due to α-thalassaemia trait. Depending on the mother's ethnic group, it may be an insignificant finding or have important health implications (Petrou *et al.* in preparation).

Risk of α-thalassaemia hydrops fetalis should be suspected when partners of Southeast Asian or eastern Mediterranean origin both have marked microcytosis with a low or normal Hb A_2. Such couples should be referred immediately for expert assessment and counselling. Definitive carrier diagnosis is by DNA studies*. In view of the hopeless prognosis for the fetus and the risks for the mother in α-thalassaemia hydrops fetalis, most informed at-risk couples choose prenatal diagnosis and request termination of pregnancy when an affected fetus is identified. Prenatal diagnosis is indicated at any stage of pregnancy but obviously the earlier the better. It is possible from 9 weeks of pregnancy onwards by CVS and DNA studies (Old *et al.* 1986), or in the second trimester by fetal blood sampling and haemoglobin electrophoresis and/or globin biosynthesis studies (Matsakis *et al.* 1980). There are reports from the United States of two affected fetuses managed by early birth and immediate exchange transfusion, followed by regular blood transfusion and iron chelation therapy as for β thalassaemia major (Beaudry *et al.* 1986; Bianchi *et al.* 1986). The long term outcome in these children will be of interest, in view of a Thai report that brain growth is usually severely retarded *in utero* (WHO 1990) this option should be considered with great caution.

This report of 18 couples at risk for offspring with α-thalassaemia hydrops fetalis and 28 prenatal diagnoses performed for them shows that mothers have suffered avoidable stillbirths and complications of pregnancy because relatively few at-risk couples were detected before the birth of one or more affected infants.

Subjects and methods

From 1982 to the end of 1991, 18 couples resident in the UK and at risk of having children with α-thalassaemia hydrops fetalis attended the Obstetric Unit at University College Hospital (London) for counselling and the offer of prenatal diagnosis. Fourteen lived in north London and four in other cities. All but one of the women were already pregnant. Most were seen within 2–3 days of referral and all within a week. Standard notes kept for each couple include the information provided by the referring centre, ethnic group, gestation when the woman was first seen, results of subsequent investigations, details of how and when the couple found they were carriers and heard of prenatal diagnosis, full obstetric history, details of choice made (with reasons when given), and details of each prenatal diagnosis. The data were tabulated on a yearly basis. The obstetric history was divided into two sections, before and after 1980, by which time screening and prenatal diagnosis for haemoglobin disorders were well established within the NHS (Modell *et al.* 1980).

Results

Fourteen of the 18 at risk couples were of Chinese, one of

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Table 1. Red cell MCH, MCV and HbA$_2$ levels in carriers of alpha zero thalassaemia trait undergoing prenatal diagnosis $n = 22$

MCV	MCH	Hb A$_2$
Range 59·4–73·0	Range 20·2–23·8	Range 1·2–2·6
66·3 SD 3·8	21·6 SD 1·06	2·16 SD 0·35
SE 1·06	SE 0·27	SE 0·1

Vietnamese and three of Cypriot extraction. Table 1 shows the relevant red cell indices and Hb A$_2$ values of the 22 parents for whom this information was in the notes. All except one had mean cell haemoglobin <24 pg and a mean cell volume <75 fl.

Table 2 summarises the couples' obstetric history. There had been 10 pregnancies before 1980 when counselling and prenatal diagnosis were not generally available, and five had led to a hydropic stillbirth or neonatal death (two women had had two). Since 1980 the couples have had 45 pregnancies, but their risk remained undetected in 16, and nine of these (eight women) ended in delivery of a hydropic baby. Even so, the risk of five of these eight women was identified only in a subsequent pregnancy by antenatal screening, plus the obstetric history. Only five at-risk couples (25%) were detected prospectively. The latest unexpected stillbirth was in 1989.

Only limited information was available on the total of 14 pregnancies that ended with the birth of a hydropic infant. Gestation at intrauterine death, stillbirth or neonatal death ranged from 26–40 weeks; two fetuses were reported to have 'congenital anomalies'; two mothers had eclampsia and at least one had a caesarean section.

Prenatal diagnosis was requested in 28 of the 29 pregnancies known to be at risk. Before 1984, it was done in the midtrimester by fetal blood sampling. First trimester prenatal diagnosis by chorion villus sampling and DNA analysis which was introduced in 1982 (Old *et al.* 1982) is always possible for α-thalassaemia, but only 9 of the 15 diagnoses since 1985 have been done in the first trimester because of late recognition of the mother's risk. In the early days of first trimester prenatal diagnosis, there was one miscarriage related to the procedure; and one misdiagnosis led to the birth of a third affected infant to the same mother. Twenty healthy infants have been born and six affected pregnancies terminated.

The following case history is given because it illustrates the problems of diagnosis and of understanding that may be encountered; similar problems have occurred for other couples at risk. Mrs. Y and her husband are from Hong Kong and neither speaks good English. Her first pregnancy in 1982 ended in a neonatal death; no diagnosis was made. Her second pregnancy in 1984 resulted in a healthy child. Her risk was first detected in 1985 at 19 weeks in her third pregnancy by routine antenatal screening. She was referred to University College Hospital for counselling, but she refused prenatal diagnosis because of the risk to the pregnancy in view of her previous stillbirth. The pregnancy ended unfortunately in a second neonatal death at 32 weeks. In her fourth pregnancy she changed both GP and hospital because of her unhappy obstetric history with the result that her notes were not available to her new GP. The couple attended as soon as a pregnancy was suspected and asked for prenatal diagnosis, but because of language problems and the lack of previous notes they were thought to be asking for termination of pregnancy; valuable weeks were lost while they were seen by a gynaecologist and managed to clarify that they did not want an abortion. As soon as they reached the antenatal clinic they requested prenatal diagnosis but were thought to be requesting exclusion of Down's syndrome. Their risk of α-thalassaemia hydrops fetalis was recognised only by routine antenatal screening. They finally arrived for prenatal diagnosis only at 16 weeks' gestation, and the third affected pregnancy was diagnosed only at 17 weeks' gestation. The couple requested termination of pregnancy but were extremely distressed, and the mother decided to be sterilised. Though fetal blood sampling in the course of termination showed an Hb of 7·6 g/dL, ultrasound examination showed only a large placenta, hyperdynamic circulation, and dilated umbilical and hepatic veins. There was no fetal oedema.

Discussion

Alpha thalassaemia is the most important genetic risk and

Table 2. Obstetric history of 18 couples at risk for alpha thalassaemia hydrops fetalis, seen for genetic counselling at UCH.

Obstetric history	Before 1980 (PND under development) *n*	After 1980 (PND established) *n*	Total *n*
At risk couples counselled	0	18	18
Viable pregnancies	10	45	55
Risk not detected: Viable pregnancies	10	16	26
Outcome:			
healthy baby	5	7	12
alpha thalassaemia hydrops	5	9	14
Risk detected: counselled			
Viable pregnancies		29	29
PND requested		28	28
Outcome:			
spontaneous abortion		1	1
TOP for alpha thalassaemia		6	6
healthy baby		20	20
alpha thalassaemia hydrops		2[a]	2

[a] One misdiagnosis and one born after prenatal diagnosis refused.

the commonest cause of hydrops fetalis in people of Southeast Asian extraction in whom the Rh negative gene is very uncommon. Alpha thalassaemia hydrops fetalis is uncommon in the UK, but most cases occur in the relatively small, easily identified groups of women of Southeast Asian or Cypriot extraction. It is important to detect couples at risk of α-thalassaemia hydrops fetalis because of the hopeless prognosis for an affected fetus, and the possibility of life threatening obstetric risks for the mother: two of the women seen by us had actually developed eclampsia in a previous pregnancy. In addition to the 6% of people of southern Chinese origin who carry α^0 thalassaemia trait (Petrou *et al.* in preparation), 3% carry β thalassaemia trait (Choi & Necheles 1983). If a woman of Southeast Asian or Cypriot origin has marked microcytosis and a raised Hb A_2 level she has β-thalassaemia trait; if she has a low or normal Hb A_2 level, she may have α-thalassaemia trait. In any case, her partner should be tested. Couples who both have such characteristics should be referred for further investigation by DNA studies, genetic counselling, and the offer of prenatal diagnosis when appropriate.

The obstetric history of families coming for prenatal diagnosis of α-thalassaemia shows poor awareness of the condition among both obstetricians and pathologists. Over two-thirds of couples having prenatal diagnosis for β-thalassaemia major at our centre have been detected by antenatal screening before giving birth to an affected child (Petrou *et al.* in preparation). By contrast, only six of 18 couples (30%) at risk for α-thalassaemia hydrops fetalis were detected before they had given birth to a hydropic infant. Even the delivery of the first hydropic infant did not necessarily lead to correct diagnosis and identification of future risk. Four couples were identified only after the birth of the first affected infant; three were identified only after the second affected birth, and five were identified only in a subsequent pregnancy by routine antenatal carrier screening plus the obstetric history.

With increasing use of routine fetal anomaly scanning, more affected pregnancies may be detected in the midtrimester although not all affected fetuses are hydropic at this stage, early signs are a big placenta, and dilatation of the hepatic vein (Kanokpongsukdi *et al.* 1990).

Informed couples at risk almost always request prenatal diagnosis, so referrals should be four times the number of affected pregnancies. We know of at least 16 affected pregnancies since 1980, mainly in north London, and as all affected stillbirths are not correctly diagnosed, the true figure is probably higher. Certainly not all couples at risk are identified. For example, Table 2 shows that the fetus was affected in nine of the 16 viable pregnancies in which risk was not detected. This deviation from the expected 25% ratio shows that the couples have been selected retrospectively, i.e. because they had one or more affected fetuses. It implies that couples at-risk whose pregnancy ends in a normal infant are being missed. The referral rate for counselling should be four times the rate of affected pregnancies and we estimate that there should be at least six referrals for prenatal diagnosis to our centre annually; however, the average is just over two. It seems likely therefore that only about half the couples at risk for α-thalassaemia hydrops fetalis in north London are being identified at present, and, in view of the relatively small number of prenatal diagnoses done for this indication elsewhere the situation is probably worse in other parts of the country.

To improve the frequency of prospective diagnosis of couples at risk for α-thalassaemia hydrops fetalis and the offer of timely prenatal diagnosis we suggest:

1. All pregnant women of Chinese or other Southeast Asian or Cypriot extraction should be specifically screened for α^0 thalassaemia trait. This is even more important if the obstetric history includes a stillbirth or neonatal death.
2. Alpha-thalassaemia hydrops fetalis should be suspected whenever such a woman has a stillbirth or neonatal death, or a history of stillbirth or neonatal death, with or without congenital malformations. Unless α^0 thalassaemia is already excluded by other findings, cord blood should be sent to the haematology laboratory for haemoglobin electrophoresis.
3. When midtrimester fetal anomaly scanning suggests fetal anaemia or hydrops in a woman of Chinese or other Southeast Asian or Cypriot origin, blood from the parents should be sent for screening for α-thalassaemia trait.
4. When a woman of Chinese or other Southeast Asian or Cypriot origin develops pre-eclampsia, α thalassaemia should be suspected, blood sent for testing and an ultrasound assessment performed.

All at risk couples detected should be offered prenatal diagnosis and selective abortion, regardless of the stage of the pregnancy.

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GYNAECOLOGY

Histological incomplete excision of CIN after large loop excision of the transformation zone (LLETZ) merits careful follow up, not retreatment

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ABSTRACT

Objective To quantify and analyse the influence of a histological report of incomplete excision of CIN after LLETZ on frequency of detection of residual CIN.
Design Review of a computerised database of sequential women treated by LLETZ. Initial follow-up was three months post-treatment.
Setting The Colposcopy Clinic, Regional Department of Gynaecological Oncology, Queen Elizabeth Hospital, Gateshead, Tyne and Wear, UK.
Subjects 721 women with CIN diagnosed histologically on LLETZ specimens.
Results In spite of a first time treatment success rate of 95% at 3 months, only 56% of the women were reported to have complete histological excision of CIN. A report suggesting incomplete excision was more likely with more severe CIN, extensive lesions and involvement of the endocervical canal. Furthermore, 21% with residual CIN had apparent complete excision of CIN at LLETZ.
Conclusions A histological report of incomplete excision of CIN at LLETZ does not equate with residual disease. The high treatment success rate of LLETZ means that a report of incomplete excision should stimulate close colposcopic and cytologic follow-up to identify the small number of women with residual CIN after therapy.

Histological examination may suggest incomplete excision of cervical intraepithelial neoplasia (CIN) after both knife conisation (Buxton *et al.* 1987) and laser conisation (Andersen *et al.* 1990). The consensus view for both these methods of treatment is that, while residual disease is found more frequently after incomplete rather than complete histological excision, it is justified to adopt an expectant approach to follow-up. LLETZ has been developed (Prendiville *et al.* 1986; Prendiville *et al.* 1989) and extensively tested (Luesley *et al.* 1990; Murdoch *et al.* 1991) for the management of CIN. In our initial report (Murdoch *et al.* 1991), we noted a discrepancy between the histological observation of apparent incomplete excision of CIN and the subsequent detection of residual CIN. We now present a detailed analysis of the significance of histological incomplete excision of CIN and consequent modifications of our management protocol.

Subjects and methods

Between 12 September 1988 and 31 May 1991, 1277 women had LLETZ performed in the Regional Department of Gynaecological Oncology, Gateshead, because of abnormal cervical cytology and/or clinically abnormal cervices. Of these, 794 had a loop specimen containing histologically identified CIN. In the remainder, the pre-treatment punch biopsy contained CIN: either the loop specimen contained no residual disease, or the loop specimen contained microinvasive or invasive squamous carcinoma, adenocarcinoma *in situ* or invasive adenocarcinoma, noncondylomatous wart virus infection, inflammation or squamous metaplasia. Seventy-three of the women who had CIN had had either only a loop biopsy or a loop/laser 'top-hat' (ie, loop excision of the centre of a lesion with laser vaporisation of peripheral extensions of acetowhite epithelium. The remaining 721 had LLETZ with the intention of therapeutic complete excision of CIN. These comprise the study group.

Colposcopy and loop diathermy treatments were performed as previously described (Murdoch *et al.* 1991). The women were reviewed in the colposcopy clinic three months after treatment. Only one defaulted from follow up. Initially, all had colposcopy and cervical cytology using the Ayres spatula. Selected women with histological evidence of incomplete excision at the endocervical margin of the loop specimen also had endocervical brush cytology performed. Others, with histological evidence of complete excision of CIN, were followed up with cervical cytology only and did not have colposcopy, in accordance with our own experience following laser ablation (Lopes *et al.* 1990) and the NHS Cervical

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Table 1. Correlation between the site of acetowhite epithelium, the histological report of the excision margins and occurrence of residual disease at follow-up at three months.

Acetowhite epithelium	Excision complete *n*	Excision incomplete *n* Endo[a]	Ecto[b]	Both[c]	NS[d]	Not stated[e]	Total All excisions *n*	Residual CIN
Ectocervical	244	40	18	19	50	33	404	12
Endocervical	99	37	4	4	32	13	189	7
Endocervical	62	29	4	5	14	14	128	14
Total *n*	405	106	26	28	96	60	721	33

[a] Histological excision incomplete at the endocervical margin

[b] Histological excision incomplete at the ectocervical margin.

[c] Histological excision incomplete at the ectocervical and endocervical margin.

[d] Excision incomplete but margin not specified.

[e] No comment made about excision margins.

Screening Programme National Coordinating Network Guidelines (personal communication, I. D. Duncan). Residual CIN was diagnosed by cervical punch biopsy, repeat LLETZ or simple abdominal hysterectomy, where appropriate.

Results

Residual CIN was identified at follow-up at three months in 33/721 (4·6%) of the women. The relation between the site of acetowhite epithelium (ectocervical or endocervical), excision margins and residual disease is shown in Table 1. Complete excision of CIN was specifically reported in 405/721 (56·2%). Incomplete excision at the endocervical margins was specifically noted in 59/404 (14·6%; 95%CI 11·2%–18·0%)—ie 40 incomplete excisions at the endocervical margin plus 19 incomplete excisions at both endocervical and ectocervical margins, when acetowhite epithelium was only on the ectocervix; in 41/189 (21·6%; 95%CI 15·7%–27.5%) ie 37 incomplete excisions at the endocervical margin plus 4 at both the endocervical and ectocervical margins, when acetowhite epithelium was in the endocervical canal with the upper limit visible and in 34/128 (26·5%; 95%CI 18·9%–34·1%) ie 29 incomplete excisions at the endocervical margin plus 5 at both the endocervical and ectocervical margins, when the upper limit was not visible. Residual CIN in the same three groups was identified in 12/404 (3·0%; 95%CI 1·3%–4.7%); 7/189 (3·7%; 95%CI 1·0%–6·4%); and 14/128 (10·9%; 95%CI 5·5%–16·3%), respectively.

The grade of CIN was related to the appearance of the excision margins in Table 2. For CIN 1 complete excision was reported in 63/87 (74·2%; 95%CI 63·0%–83·4%); for CIN 2 complete excision was reported in 69/112 (61·6%; 95%CI 52·6%–70·6%) cases; and for CIN 3, complete excision was reported in 273/552 (53·3%; 95%CI 49·1%–57·5%). Although residual disease was detected rarely with CIN 1 (1·1%; 95%CI –1·1%–3·3%), there was no difference in the rates of residual disease with CIN 2 (5·4%; 95%CI 1·2%–9·6%) and CIN 3 (4·7%; 95%CI 2·9%–6·5%). Finally, the relation between the histological report of the excision margins and residual disease is found in Table 3.

Discussion

It is not surprising that apparent incomplete excision of CIN and the detection of residual CIN occurred more often with the more severe, more extensive lesions that were sited within the endocervical canal. For such lesions we perform

Table 2. Correlation between grade of CIN, and a histological report of incomplete excision and residual CIN.

Histology	Excision complete *n*	Excision incomplete *n* Endo[a]	Ecto[b]	Both[c]	NS[d]	Not stated[e]	Total CIN 1, 2, 3	Residual CIN
CIN 1	63	2	1	0	10	11	87	1 (1·1%)
CIN 2	69	8	1	2	21	11	112	6 (5·4%)
CIN 3	273	96	24	26	65	38	522	26 (4·7%)
Total *n*	405	106	26	28	96	60	721	33 (4·6%)

[a] Histological excision incomplete at the endocervical margin.

[b] Histological excision incomplete at the ectocervical margin.

[c] Histological excision incomplete at the ectocervical and endocervical margin.

[d] Excision incomplete but margin not specified.

[e] No comment made about excision margins.

Table 3. Relation between the histological report of the excision margins and residual CIN.

Report	*n*	Residual	%	95%CI
Complete	405	7	1·7	0·4 to 3·0
Incomplete endo[a]	106	10	9·4	3·9 to 14·9
Incomplete ecto[b]	26	2	7·7	−2·5 to 17·9
Incomplete both[c]	28	10	35 7	18·0 to 53·4
Incomplete NS[d]	96	4	4·2	0·2 to 8·2
Not stated[e]	60	–	–	–

[a] Histological excision incomplete at the endocervical margin.
[b] Histological excision incomplete at the ectocervical margin.
[c] Histological excision incomplete at the ectocervical and endocervical margin.
[d] Excision incomplete but margin not specified.
[e] No comment made about excision margins.

loop conisation, aiming to achieve a cone length of 2 cm (Mor-Yosef *et al.* 1990). A histological report of incomplete excision clearly increased the risk of residual disease and this was greatest when extensive lesions reached both the ectocervical and endocervical excision margins. Despite this, however, residual disease was identified only in a small number of those in whom incomplete excision was reported. Although only 56% of our patients were specifically reported as having complete excision, our first treatment success rate was 95%. Additionally, in 7/33 (21%) recurrent CIN occurred when the histological report had suggested complete excision. Clearly, histological incomplete excision does not equate with residual disease at three months.

There are several reasons for this discrepancy. Firstly, colposcopically directed LLETZ allows precise removal of acetowhite epithelium with minimal excision of normal tissue at the edge of a lesion. Thermal destruction of healthy marginal tissue in the specimen will result in lesions reaching the edge of specimens submitted for histology even though excision has been complete. Secondly, we use ball coagulation diathermy extensively in the loop base, primarily to establish effective haemostasis. An inevitable side effect of this is further destruction of tissue in the loop base, providing an extra margin of safety. Thirdly, it is possible that the host inflammatory response to LLETZ may result in resolution of residual CIN at the treatment margins.

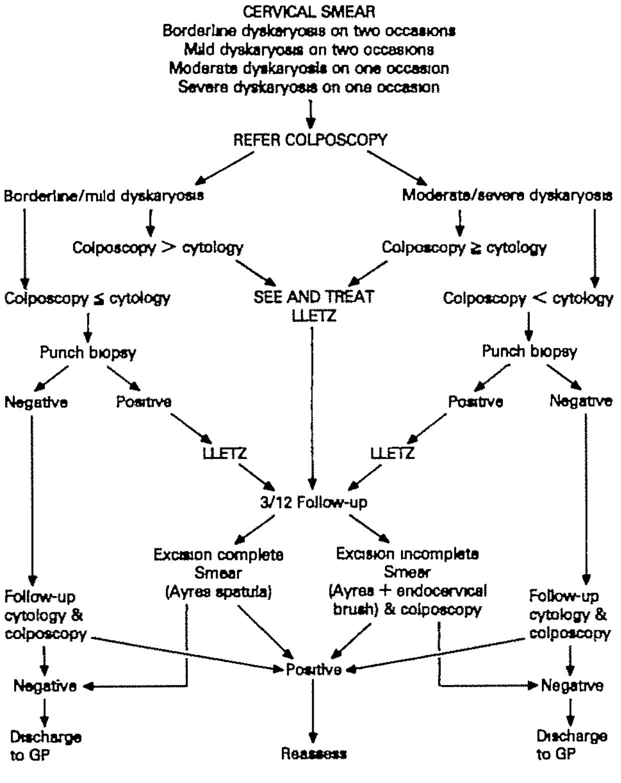

Fig. 1. Algorithm for management of patients with abnormal cervical cytology using LLETZ with a 'see and treat' policy.

In view of these findings, we have modified our evolving management algorithm to target women most likely to have residual CIN after LLETZ (Fig. 1). This allows us to identify accurately those with residual CIN without subjecting adequately treated patients to unnecessary second procedures.

In 96 cases, the histologist reported incomplete excision but was unable to comment upon which margin was involved. This was due to fragmentation of the specimen that prevented accurate orientation. In a further 60 cases the histologist made no comment on the excision margins. This information is important as it affects the likelihood of residual CIN being present and the method of follow up required. For the purposes of follow up, both these groups were regarded as having incomplete excision of CIN. It is likely, however, that the group of patients in whom no comment was made on histological excision margins had, in fact, had complete excision of CIN as none of them had residual CIN on follow up.

In our department we have enthusiastically adopted a 'see and treat' policy since adopting LLETZ, virtually exclusively, for the management of CIN. We have found it to be safe, effective, efficient and highly acceptable to patient and colposcopist alike (Murdoch *et al.* 1991; Murdoch *et al.* in press). This policy has been a major contributor to the efficiency with which our colposcopy clinic is run. Using a clinic with two examination couches, our maximum delay from receipt of a referral letter to attendance at the clinic is three weeks, irrespective of the severity of the referral smear. In the year 1990–1991 we performed 513 LLETZ procedures. An initial high rate of histologically negative LLETZ specimens has been addressed by restricting 'see and treat' management to patients with moderate or severe dyskaryosis and compatible colposcopic appearances and to those with mild dyskaryosis and colposcopy suggesting definite CIN.

After treatment, we have found that only one of the 33 residual CIN lesions was missed at follow-up by cervical cytology. This case was identified because colposcpy on the same occasion revealed acetowhite epithelium on the cervix. We have, consequently, extended our established post-laser ablation follow up policy to women having complete excision with LLETZ; both now have cervical cytology and the colposcope is not used. However, if incomplete excision is reported, follow up includes colposcopy with ectocervical and endocervical brush cytology in view of the higher risk of residual CIN. The reliance on follow-up cytology alone in over half our treated cases further enhances the efficient through-put of patients.

We believe that LLETZ is the treatment of choice for management of CIN and that a histological report of incomplete excision of CIN should stimulate more detailed follow up to identify the small number of patients who do, in fact, have residual disease.

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GYNAECOLOGY

A longitudinal study of pelvic inflammatory disease

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ABSTRACT

Objective To study the microbiology and long term prognosis of pelvic inflammatory disease (PID).
Design A prospective study of women with laparoscopically confirmed PID.
Setting Teaching hospital in central London.
Subjects 23 women with PID.
Outcome measures Microbiological investigations at the time of diagnosis and at follow up; subsequent fertility and the occurrence of pelvic pain.
Results PID diagnosed by laparoscopy was regarded as moderate to severe in 15 cases. *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma hominis* and *Ureaplasma urealyticum* or a combination of these micro-organisms were detected most frequently in the cervix, less often in the endometrium and least in the tubes, *C trachomatis* being the micro-organism found most commonly in the tubes. There was serological evidence of acute chlamydial infection in 13 of 20 cases in which paired sera were available and a serological response to *M. hominis* in 9 of 12 cases in which it was possible to evaluate the results. On the basis of microbiological and serological results, *C. trachomatis* appeared to be the most important aetiological agent in 10 cases, *N. gonorrhoeae* in four cases, *M. hominis* in three cases and *U. urealyticum* in none; in five cases, two of these micro-organisms appeared to be of equal importance. After 1 to 3 years, 33% of the women were having difficulty conceiving and 56% continued to complain of pelvic pain.
Conclusion It is difficult to be certain of the infectious cause of PID in any given case. However, the evidence that *N. gonorrhoeae* and *C. trachomatis* are pathogens is very strong. *M. hominis* may be responsible for a few cases on its own or together with other micro-organisms.

The importance of the effects of pelvic inflammatory disease (PID) on Western society is demonstrated by the demand for treatment of tubal infertility (Hull *et al.* 1985). The natural history of the condition is still incompletely understood, and although various agents each have been shown to be involved in its pathogenesis (Mårdh 1980), PID is often thought to be of polymicrobial aetiology (Eschenbach *et al.* 1975). It has been postulated that the organisms causing the damage differ during the course of the infection (Weström 1987), the disease being initiated by the most pathogenic organisms, such as *N. gonorrhoeae* and maintained by secondary invaders such as anaerobes. Thus both serological techniques and detection of organisms may be required to determine the aetiology of the infection in any given case.

In this study we have attempted to establish the cause of the infection in 23 cases of laparoscopically proven PID by taking samples directly from the lower and upper genital tracts and examining paired sera for quantitative estimation of antibody. We measured outcome in the short term by clinical assessment and repeat laparoscopy, and in the long term by assessment of symptoms and fecundity.

Subjects and methods

Study population

Women presenting with lower abdominal pain to the sexually transmitted diseases clinic (Praed Street, London) or the acute gynaecological unit (Samaritan Hospital, London) during the period November 1984 to August 1987, were studied. Permission to undertake the study had been granted by

Correspondence: Professor D. Taylor-Robinson, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ the Ethics Committee at St Mary's Hospital. If a diagnosis of PID was suspected on clinical grounds and informed consent was given by the woman, a laparoscopy was performed. Thus the women were a self-selected group who chose such investigation as opposed to presumptive antibiotic treatment. Of 112 women studied, only 22 had the diagnosis of PID confirmed at laparoscopy. One woman had two episodes of PID during the study period, and these were counted as two separate events. Thus there were 23 cases of PID which are described here.

Consorts and clinical assessment

A detailed sexual history was taken from the women, and their partners were advised to attend the clinic for screening. A full history was taken, and general and gynaecological examinations were performed prior to laparoscopy.

Laparoscopic diagnosis

The diagnosis of PID was made laparoscopically and the inflammation was graded as mild, moderate or severe (Hager *et al.* 1983). Mild inflammation was characterised by swollen, erythematous Fallopian tubes that were freely moveable, even if there were filmy adhesions present. In moderate disease there was also a sticky exudate in the peritoneal cavity, but fibrous adhesions were not invariably present. In severe disease it was difficult to identify all the pelvic structures fully because of gross adhesions. Adhesions were graded for severity by inspection and manipulation of the tubes at laparoscopy. Mild adhesions were filmy and did not grossly obstruct tubal motility, whereas severe adhesions were fibrous and prevented any movement of the tube. Moderate adhesions were between these two extremes. If the disease was asymmetrical, its severity on the worse affected side was noted.

Specimen collection

Laparoscopy was performed, if possible, before any antibiotics had been given. However, in four cases samples from the lower genital tract and the endometrium were taken before treatment and samples from the Fallopian tube were taken after one or two doses of antibiotic:

1. Lower genital tract: Cotton tipped swabs were used to collect material from the cervix and urethra. This was inoculated immediately onto agar plates for culture of *N gonorrhoeae* (Ison *et al.* 1987). Additional specimens were taken for gram staining, microscopy and for the detection of *C. trachomatis* by the MicroTrak (Syva, Maidenhead, Berks, UK) direct fluorescent antibody (DFA) test (Thomas *et al.* 1984). In addition, material from two separate cervical swabs was expressed in mycoplasma and chlamydia transport medium. Sufficient material was available to provide adequate specimens for these tests.
2. Upper genital tract: Endometrial samples were taken transcervically using a guarded curette (Kriseman 1982) to prevent contamination of the specimens during passage through the cervix. Divided specimens of endometrium were distributed to agar plates for detection of *N. gonorrhoeae*, MicroTrak slides for *C. trachomatis* and vials of transport medium for mycoplasmas and anaerobes. The Fallopian tubes were sampled via a cannula inserted into a second portal (Nordvall 1970).

   Three swabs were taken from the fimbrial end of each tube. The first swab was used to inoculate an agar plate and was then expressed in chlamydia transport medium. The second was rubbed on a MicroTrak slide and then expressed in mycoplasma transport medium, and the third was placed directly into transport medium for anaerobes.
3. Serology: Serum was saved at the time of the initial laparoscopy and at subsequent visits.

Laboratory investigations

The agar plates were incubated in an atmosphere of 6% CO_2 in air for 48 h and then examined for colonies of *N. gonorrhoeae. C. trachomatis* was identified by the MicroTrak test and smears containing at least one elementary body were considered positive (Thomas *et al.* 1984). *M. hominis* and *U. urealyticum* were isolated in liquid growth medium containing arginine or urea, respectively (Taylor-Robinson & Furr 1981).

Gardnerella vaginalis was isolated on 5% human blood agar with the addition of gentamicin, nalidixic acid and amphotericin (Ison *et al.* 1982). Anaerobic bacteria were isolated on reinforced clostridial agar supplemented with 1% liver digest and 5% horse blood. All samples were inoculated onto this medium with and without the addition of kanamycin (100 mg/l) and vancomycin (75 mg/l) and incubated in an anaerobic cabinet for 5 days. Anaerobes were identified by their sensitivity to metronidazole (5 μg) and by the methods described in the Anaerobe Laboratory Manual (Holdeman *et al.* 1977). *Mobiluncus* spp. were isolated and identified as described previously (Ison *et al.* 1989).

Serum antibodies to *C. trachomatis* (D-K serovars), *M. hominis* and *M. genitalium* were demonstrated by means of microimmunofluorescence (MIF) tests (Thomas *et al.* 1976, Furr & Taylor-Robinson 1984). The chlamydial serology results were interpreted as indicating acute infection if the IgM titre was 1 in ≥ 8 and/or there was a fourfold or greater rise or fall in the IgG titre, and chronic infection if there were stable high titres of IgG (1 in ≥ 256). The *M. hominis* and *M. genitalium* serology results were considered to indicate acute infection if there was a fourfold or greater rise or fall in the IgG titre.

Means of interpreting microbiological and serological results combined

The likelihood of each micro-organism being responsible for PID, based on their known pathogenic potential combined with serological evidence of acute infection, is postulated in Table 1. This arbitrary assessment provides a means by which the role of one micro-organism relative to that of others in a mixed infection may be evaluated. Anaerobes and other micro-organisms involved in bacterial vaginosis are not represented in Table 1 because they were recovered so rarely (never from the Fallopian tubes) in this study (see Microbiological findings, page 996, in this article).

Table 1. Assessment of the likelihood of each micro-organism causing pelvic inflammatory disease. 4 = very strong; 3 = strong; 2 = moderate; 1 = weak.

Presence of micro-organism	Antibody response	Likelihood of causing disease
N. gonorrhoeae		
Upper tract	—	4
Lower tract	—	3
C trachomatis		
Upper tract	Positive	4
Upper tract	—	3
Lower tract	Positive	3
Lower tract	—	2
Not detected	Positive	2
M. hominis		
Upper tract	Positive	3
Upper tract	—	2
Lower tract	Positive	2
Lower tract	—	—
Not detected	Positive	1
U. urealyticum		
Upper tract	—	1
Lower tract	—	—

Treatment

The antibiotics (see Results below) used in each case were determined by the micro-organisms detected and the condition of the patient. Treatment for at least one week was prescribed initially.

Follow up

The women were kept in hospital until their symptoms had improved, and they were then seen weekly in the clinic. Regular vaginal examinations were performed to assess the degree of tenderness and swabs were taken from the lower genital tract to determine whether pathogens had disappeared. After 6 weeks, a repeat laparoscopy was offered to assess the response to treatment. The women were encouraged to attend the clinic early if their symptoms recurred.

Long term evaluation was undertaken by examining the patient's hospital notes, and a questionnaire about fertility and symptoms was sent to all participants approximately 3 years after the completion of the study.

Results

Laparoscopic findings

In the 23 cases of PID, inflammation was classified as mild in 8, moderate in 11 and severe in 4. Adhesions were graded as mild in 9, moderate in 6 and severe in 4 and were not seen in 4 cases at the time of the initial laparoscopy (Table 2).

Microbiological findings

N. gonorrhoeae, C. trachomatis, M. hominis and *U. urealyticum* were discovered in the cervix (Table 3) as follows: all four were found in two cases, three in seven cases, two in three cases, one in eight cases and none in only three cases. In

Table 2. Laparoscopic findings, treatment and follow up in 23 cases of PID. D = doxycycline; M = metronidazole; S = spectinomycin, A = ampicillin or amoxycillin; C = ceftriaxone; E = erythromycin, ? = not exposed to risk of pregnancy; NA = information not available or unknown.

Case no.	Initial laparoscopy: Inflammation*	Initial laparoscopy: Adhesions**	Repeat laparoscopy	Treatment	Reproductive outcome	Symptomatic outcome
1	2	1		D,M,A,	Subfertile	Recurrent PID
2	1	0		D,M	NA	NA
3	3	3	Severe adhesions	D,M	?	Recurrent pain
4	2	1	Mild adhesions	C	?	Asymptomatic
5	2	0		C	Pregnant	NA
6	3	3		D,M,S	NA	NA
7	3	2		C	Subfertile	Recurrent pain
8	2	2		D,M,S	Pregnant	Asymptomatic
9	2	3		D,C	NA	NA
10	1	1		D,M	NA	Recurrent pain
11	2	2	Severe adhesions hydrosalpinges	C	?	Recurrent pain
12	2	0	Mild adhesions	C,E	?	Asymptomatic
13	1	0	Moderate adhesions	D,C	Pregnant	Recurrent pain
14	1	1	Normal	D,M,S	?	Asymptomatic
15	1	1	Mild adhesions	D,M	?	NA
16	3	3		D,M,S	NA	Asymptomatic
17	2	2	Moderate adhesions	D,M,S	NA	Asymptomatic
18	1	1		D,M	Subfertile	Recurrent pain
19	2	1		D,M	NA	NA
20	1	1	Mild adhesions	D,M,S	Pregnant	Recurrent pain
21	1	2	Moderate adhesions	M,A	Pregnant	Recurrent pain
22	2	2		D,M	NA	Asymptomatic
23	2	1		C	NA	Recurrent pain

*1–3 = mild to severe inflammation.
**0–3 = none to severe adhesions.

Table 3. Organisms, serology and postulated aetiology in 23 cases of PID + = detected; o = not detected; – = no result or not tested; N = *Neisseria gonorrhoeae*; C = *Chlamydia trachomatis*; M = *Mycoplasma hominis*; U = *Ureaplasma urealyticum*.

	Organisms				Serology*						
					C trachomatis		*M. hominis*				
Case no.	Cervix NCMU	Endometrium NCMU	Tubes NCMU	Partner	IgM	IgG	IgG	Postulated** aetiology			
1	+o++	oo++	oooo	N	16/8	512/512	64/≥256	N3	M3	C2	U1
2	o+oo	o++o	o+oo	nil	0	0		C3	M2		
3	o+++	o+oo	oooo	—	16/16	256/1024	8/128	C4	M2		
4	oo++	oooo	oooo	—	0/0	4/8	>256/128	M2			
5	ooo+	ooo+	oooo	—	0/0	16/32	16/64	M1	U1		
6	oo+o	oo+o	oooo	—	0	16		M2			
7	+o++	+o++	oooo	—	32/8	≥2048/512		N4	C2	M2	U1
8	o++o	o+oo	oooo	C	0/0	256/512	16/64	C3	M2		
9	++++	o+oo	oooo	NC	32/64	1024/128	16/64	C4	N3		M2
10	o+oo	oooo	oooo	nil	4	256/512		C2			
11	+o––	––––	––––	N	4/4	128/>256	64/32	N3	C2		
12	o++o	o+oo	o+oo	C	8/8	256/256		C4			
13	o+++	ooo+	o++o	nil	0/0	256/256	2/64	C3	M3	U1	
14	o+oo	o+oo	o+oo	nil	0/0	16/64	8/16	C4			
15	ooo+	–ooo	–ooo	—	16/8	1024/>2048	4/64	C2	M1		
16	o+oo	–ooo	––+oo	C	0/0	128/1024	8	C4			
17	++++	++++	+ooo	N	4/8	128/256	32/32	N4	C4	M2	U1
18	oooo	–ooo	–ooo	—	0	8		—			
19	oooo	oooo	oooo	—	0/0	0/0	8/32	M1			
20	+o++	oooo	oooo	nil	0/0	2048/2048		N3			
21	oooo	oooo	oooo	—	16	512		C2			
22	o+++	oo++	oooo	—	16	512/512		C2	M2	U1	
23	+o++	–o++	–ooo	N	8	512		N3	C2	M2	U1

*Titre = 1/number stated.

**Letters = abbreviations of organisms; numbers correspond to likelihood expressed in Table 1.

the upper genital tract, the majority of these micro-organisms occurred in the endometrium, few being found in the tubes other than *C. trachomatis*. The distribution of the various micro-organisms at the different anatomical sites is summarised in Table 4.

In addition to the four micro-organisms mentioned, *G. vaginalis* (three cases), curved rods (two cases), anaerobes (two cases), coliforms (one case) and lactobacilli (one case) also were identified in the endometrium, but none of them occurred in the Fallopian tubes.

Serological findings

The serological results are shown in Table 3. An IgM titre of 1 in ≥ 8 to *C. trachomatis* was found in 10 cases, a fourfold or greater change in the IgG titre to *C. trachomatis* in seven cases and a stable, high IgG titre in seven cases. In five cases in which *C. trachomatis* was not detected, there was serological evidence of an acute chlamydial infection. Overall, there was serological evidence of an acute chlamydial infection in 13 of 20 cases in which either paired sera were available or IgM was detected in a single serum. A fourfold rise in titre of antibody to *M. genitalium* was found in one case (Case 3), and a fourfold or greater change to *M. hominis* in 9 of 12 cases in which it was possible to evaluate the results; in three of these, *M. hominis* had not been isolated.

Table 4. Detection of organisms at different anatomical sites in 23 cases of PID.

	Cases with micro-organisms at indicated site (*n*)		
Organism	Lower genital tract	Endometrium	Tubes
C trachomatis	11	7	5
N. gonorrhoeae	7	2	1
M. hominis	13	7	1
U. urealyticum	12	7	0
G. vaginalis	ND	3	0

ND = Not done.

Interpretation of microbiological and serological results

On the basis of the combined microbiological and serological results, *N. gonorrhoeae* and/or *C. trachomatis* were implicated in 18 (78%) of the cases (Table 3). When the postulation presented in Table 1 was applied to the microbiological and serological results for each patient, *C. trachomatis* appeared to be the most important micro-organism in 10 patients, *N. gonorrhoeae* in four cases, *M. hominis* in three (moderately strong in two but weakly in the other) and *U. urealyticum* in none (Table 3). In five cases, two micro-organisms appeared to be of equal importance.

Treatment and follow up

Fourteen women (Table 2) were treated with oral doxycycline and metronidazole. Of these, six also had a single injection of spectinomycin for known or suspected *N. gonorrhoeae* infection, and one received amoxycillin. One woman required intravenous hydration due to vomiting and was given ampicillin and metronidazole only. For eight cases (Table 2), treatment comprised an intramuscular injection of ceftriaxone administered daily for 7 days together with oral antichlamydial treatment (erythromycin or doxycycline) in three cases. After clinical improvement and completion of treatment, pathogens were not detected in the cervix of any patient. Four women were lost to subsequent follow up examination, but a repeat laparoscopy was performed on each of 10 women. There was no evidence of continuing inflammation in any of the women, and endometrial and tubal specimens were found to be microbiologically negative.

The long-term (> 1 year) symptomatic outcome is known for 16 women. Nine (56%) of them, including two women who had chronic pelvic pain before entering the study, continued to complain of pain and some were diagnosed repeatedly as having PID.

The findings at the second laparoscopy and/or the answers to the questionnaire were used to assess the reproductive outcome for 15 women. In general, the pattern of adhesions was similar to or worse than that seen during the original diagnostic laparoscopy. Two women had severe pelvic adhesions, and three others reported unsuccessful attempts to conceive, giving a subfertility rate of 5/15 (33%). Women who were regarded as fertile included those with no or mild adhesions at repeat laparoscopy (5/15), and those who had an intra-uterine pregnancy since the episode of PID (5/15 including one who also had mild adhesions at laparoscopy). Thus the number of women thought to be fertile was 9/15 (60%).

Partners

Partners were reluctant to attend the clinic but those of 12 women, including one woman who had two episodes, were examined (Table 3). *N. gonorrhoeae* alone was found in four partners, *N. gonorrhoeae* and *C. trachomatis* in one and *C. trachomatis* alone in three; these pathogens corresponded to those found in the women.

Discussion

The difficulty of making a clinical diagnosis of PID is highlighted in this study by the fact that only one-fifth of the women were confirmed as having PID at laparoscopy. It has been pointed out previously (Brihmer *et al.* 1987) that the accuracy of diagnosis is related to the severity of the signs and symptoms and it is noteworthy that most women in this study were not severely ill.

The pathogens most commonly considered to be associated with PID are *N. gonorrhoeae*, *C. trachomatis* and anaerobes. However, a precise understanding of the cause of the disease in any individual case may be difficult because these and other micro-organisms may exist in combination, not only in the lower genital tract but also in the upper tract. It is for this reason that we provided an assessment of the most likely infectious cause of the disease based on the known pathogenic potential of the micro-organisms and their site of existence as an aid to defining the most important micro-organism in each woman in our study. Although *N. gonorrhoeae* and/or *C. trachomatis* were clearly the most important causes of disease, there was some evidence to suggest that *M. hominis* may sometimes be a primary pathogen. Further evidence for the role of these micro-organisms in PID may come from a comparison of their existence in women with and without PID (data to be published). A pathogenic role for *M. genitalium* is particularly unclear because evidence for its involvement was sought by serology alone and a significant antibody response was seen in only one woman. Judgement of its significance should be suspended until samples from women have been examined microbiologically, preferably by the polymerase chain reaction (Palmer *et al.* 1991).

The proportion of severe cases of inflammation was small and may account for the failure to detect anaerobes in the upper genital tract. Nevertheless, the infrequent finding of any micro-organism in the Fallopian tubes, apart from *C. trachomatis*, was disappointing and could, in part, be due to the fact that swabbing the tubes does not provide large amounts of material for microbiological examination. The extent to which this affects our assessment of aetiology is unknown. Furthermore, an additional problem in understanding aetiology is that we have found *C. trachomatis* in the tubes of women who did not have obvious laparoscopic evidence of PID (Stacey *et al.* 1990). Of several possible explanations, the occurrence of the organisms in endosalpingitis, not visible to laparoscopic inspection of the tubes, is likely. Indeed, it is difficult in such a small study to match clinical features or laparoscopic appearances with proposed aetiological agents or stage in the disease process. Furthermore, previous exposures to different antigens may diminish the recovery of micro-organisms from the upper genital tract and influence the occurrence of irreversible tubal damage. In most cases, damage has already occurred by the time the diagnosis is made, and treatment results in damage limitation rather than cure. Thus the prognosis after a confirmed attack of PID is poor, both in terms of reproductive outcome and symptoms (Weström 1988). The frequent occurrence of chronic pain is significant because of the diagnostic difficulty that it presents in the future. The extent to which such pain is stimulated by previous pelvic infections, or is due to pelvic congestion (Beard *et al.* 1988) is worthy of exploration.

Conclusion

It is difficult to be absolutely sure of the infectious aetiology of PID in any given case. For routine care the strategy should be to seek the most common pathogens, *C. trachomatis* and *N. gonorrhoeae*, at the site where they are most accessible, namely the cervix. Examining the partner may reveal pathogens and could be particularly helpful in cases where cervical swabs have not been taken before the start of treatment. Sampling the upper genital tract, though important for research, is less likely than cervical sampling to reveal sexually transmitted agents. The evidence that *N. gonorrhoeae* and *C. trachomatis* are pathogens is overwhelming. *M. hominis* may be responsible for a few cases of acute PID either on its own, or in combination with *C. trachomatis* or *U. urealyticum*. Once the diagnosis has been confirmed, the outcome from reproductive and symptomatic standpoints is poor and future efforts should be directed at prevention rather than cure.

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CLINICAL PRACTICE

The usage of pregnancy tests in one health district

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ABSTRACT

Objective To investigate the total number of pregnancy tests performed and the proportion that are repeated in one health district. To relate these results to the number of conceptions.

Design Collection of data related to the numbers of pregnancy tests performed from all sources. Surveys of women booking for antenatal care or undergoing non-routine obstetric ultrasound examination.

Setting One health district in the south of England.

Results About five pregnancy tests were performed for each proven pregnancy. Nearly two-thirds of tests were purchased over the counter, the remainder being carried out by hospital laboratories and pregnancy advisory services. Very few women had their pregnancy diagnosed on clinical grounds alone and a small number of ultrasound examinations were apparently performed in lieu of chemical tests. Repeated testing was more likely in primiparous women ($P<0.005$).

Conclusions Chemical pregnancy tests appear to be trusted more than clinical examination for the diagnosis of pregnancy by women and doctors. When there is no medical urgency, women who want formal confirmation of pregnancy should be advised that home testing kits will provide the quickest results.

Modern, simple to perform pregnancy tests are available privately or on the National Health Service. Data on the number of pregnancy tests performed by a single laboratory are reasonably easy to obtain. The total number of tests performed from all sources, the reason for them being performed, the unnecessary repetition of tests and the cost implications to the NHS and individual are less well known.

This study reviewed pregnancy testing from all sources for the population served by one health district. Commonly used laboratory tests for pregnancy rely on antibodies that pick out the hormone, human chorionic gonadotrophin (HCG). This protein is produced by the placenta or its precursor from about seven days after fertilisation and may therefore be measured before implantation is complete. The sensitivity and specificity of immunological tests have been greatly enhanced by the use of antibodies which react with the beta-subunit of HCG. This immunoassay is a relatively cheap agglutination test and has been in wide use for some time. Newer, more sensitive and specific techniques, such as ELISA and monoclonal antibodies, are being used more often and can reliably test for pregnancy within a few days of the missed period.

This study was concerned only with testing for pregnancy, other indications for measuring levels of HCG (for example monitoring and follow-up of chorionic carcinoma) were not included.

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At the time of this study, two forms of test were offered by the local health authority laboratory: a haemagglutination test for routine requests and a more sensitive ELISA-based test for special indications such as possible ectopic pregnancy.

Method

This study looked at three different sources of pregnancy tests:

1. Assessment of the numbers of pregnancy tests sold or performed and sources of those tests in one year (1990).

A computerised list of every test and its result was obtained from the pathology laboratory that carried out the test on behalf of the health authority. Other possible sources of pregnancy tests were investigated and the number provided over 1 year obtained. If these data were not available, a figure for a shorter period was extrapolated to give the approximate figure for one year. The various establishments approached were visited mainly although several were contacted by telephone and letter. Those chemists that did not have figures available kept a log over a period of several weeks. The numbers of tests provided for health authority residents by agencies outside the district (for example The British Pregnancy Advisory Service) were also obtained.

If the figures were extrapolated it was assumed that the demand for pregnancy tests was uniform throughout the year.

Table 1. Pregnancy tests sold or performed in 1990.

Sources	*n*
Pharmacists	
Self testing kits	6917
In-house testing	232
Laboratory	
General practitioner request	3366
Hospital requests, including family planning clinics	433
Hospital doctor	120
Supermarkets	337
Pregnancy advisory services	13
Private hospital	3
Total	11 421

2. Antenatal booking patients.

All women booking for antenatal care at the only maternity hospital in the district during 10 consecutive antenatal clinics were included in the study. Although pregnancies are not equally distributed throughout the year, with the number of births peaking in September or October, it was felt that this would not seriously affect the validity of the results. A study form was completed by the midwife for each woman on her first visit. Questions were asked about age, parity, gestation and source and number of pregnancy tests performed.

3. Ultrasound examination in early pregnancy.

Some women have their pregnancy diagnosed by ultrasound without an immunological test. The ultrasonographers identified all nonroutine requests in early (i.e. before 28 weeks gestation) pregnancy. Routine antenatal scans were not included because pregnancy has been diagnosed by this stage. Indications for the request and its source, a short obstetric history, history of pregnancy testing and ultrasound diagnosis were recorded on a study form. If several differential diagnoses were given, the first was taken as the reason for the request. These details were recorded by the ultrasonographers and entered onto a log sheet.

The forms for the above studies were completed with the women's consent (none refused). Women requesting termination of pregnancy were not interviewed. In this district women admitted with bleeding in early pregnancy undergo ultrasound scanning and therefore were included in this part of the study.

After completion the results for all of the above sections were tabulated for analysis using Lotus 1-2-3 and Epi Info 5 software on an IBM PC.

Results

There were 1532 live births to district residents in the study year and a further 636 proven pregnancies which did not continue to term (OPCS Common Data Set 1991; Salisbury Health Authority 1991). The latter figure includes 314 therapeutic abortions, 22 proven ectopic pregnancies and 300 spontaneous abortions and is an underestimate because it excludes miscarriages in women in early pregnancy who were not admitted to hospital in the UK. This problem has been noted before but is difficult to quantify without knowledge of conception rates (Edmonds *et al.* 1982; Wilcox *et al.* 1988).

The total numbers of tests obtained from different sources in 1990 are shown in Table 1. Although these figures mix resident and catchment populations, this was considered to be of minor importance because it was assumed that most women obtained a test from their own general practitioner or from a chemist near to their area of residence. Addresses were not available for women who purchased their own pregnancy test.

Tests performed by the hospital laboratory

A total of 3799 pregnancy tests were performed by the laboratory which serves the hospital, general practitioners and family planning clinics. A further 120 sensitive ELISA tests were performed by hospital doctors during on-call hours.

The 3799 tests performed by laboratory staff related to 3140 patients. 1794 (47%) of these tests were negative, 73 (2%) equivocal and the remainder positive. Six hundred and fifty nine (17%) tests performed were repeat tests within a 4 month period. This period was chosen because it was presumed that tests more than 4 months apart were likely to have been for separate pregnancies. Amongst the women to whom these 659 repeated tests related, 184 had two negative tests and 167 had a negative test followed by a positive test. Most of the remainder had several negative tests followed by a positive. Twenty women had five or more tests, three of them having five or six consecutive negative tests. The number of home pregnancy tests performed by any of the women for whom a pregnancy test was requested from the laboratory was not known.

Amongst the negative tests, 111 (6%) were returned with the comment 'It's too early for a reliable result, please repeat'. For those tests performed by the laboratory staff, 3366 (89%) were requests from general practitioners and the remainder from hospital and family planning clinic staff.

Tests from pharmacists

There was a wide variation in the number of tests obtained

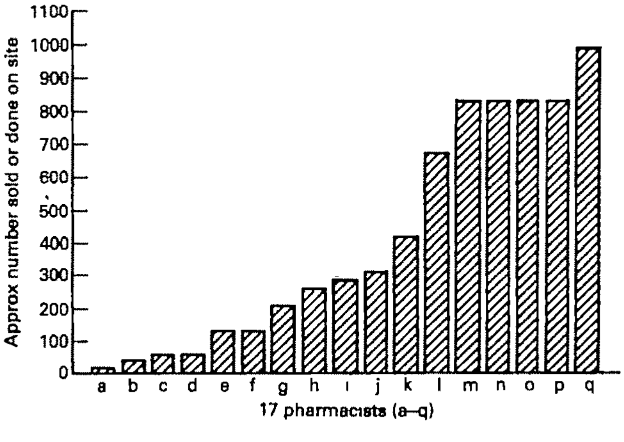

Fig. 1. Variation in numbers of pregnancy tests sold by pharmacists in the Salisbury area in 1990 (n = 6917). The numbers for letters m, n, o and p represent the total for the chain divided by 4.

Table 2. Antenatal booking clinic pregnancy tests related to age and parity (n = 145). Primiparous women were significantly more likely to have more than one pregnancy test than multiparous women ($\chi^2 = 8\cdot8$, 1 dof, $P<0\cdot005$; OR = 0·35, 95% CI 0·16–0·75). There was no significant difference between the age groups.

	Age n					Parity	
	<20	20–24	25–29	30–34	>34	Primiparous n	Multiparous n
No test	0	0	3	1	0	0	4
1 test	3	15	40	20	8	30	56
>1 test	2	16	22	9	2	31	20
Ultrasound only	0	3	1	0	0	3	1
Total	5	34	66	30	10	64	81

from different pharmacists (Fig. 1). Only four out of 20 pharmacists offered an in-house pregnancy test and all four said that they were willing to offer some counselling after the test. The cost of the test varied between about £5 and £9. There is no charge to women in this district for tests when obtained from general practitioners, the health authority (including family planning clinics) or from the pregnancy advisory services included in the study.

The results of self administered tests were not known.

Antenatal booking clinic

During the study period 145 women booked for antenatal care at 10 clinics. The number of tests for both primiparous and multiparous women is shown in Table 2. For these 145 pregnant women a total of 237 chemical pregnancy tests and seven ultrasound examinations were performed before the routine antenatal ultrasound at 16–18 weeks gestation. Of these tests, 108 (46%) were self administered. Only four out of 145 pregnant women had their pregnancy diagnosed clinically: all were multiparous and two of them booked late (>20 weeks).

Women undergoing ultrasound in early pregnancy

During the 15 weeks of this study, 91 nonroutine ultrasound examinations in early pregnancy were performed. Most requests were from general practitioners (65%) and from the gynaecology ward for in-patients (29%). The remainder were from gynaecological, antenatal and family planning clinics. The indications for requests are shown in Table 3.

A total of 17 (19%) women for whom an obstetric ultrasound examination was requested had not had a laboratory pregnancy test. Of these, six requests were to exclude ectopic pregnancy, three to confirm pregnancy, three for possible spontaneous abortion (two of whom were not pregnant on ultrasound) and two for back pain and vaginal bleeding. The remainder were for different indications.

Table 3. Indications for ultrasound request (n = 91).

Indication	Requests n	(%)
? Pregnant	32	(35)
? Ectopic, including previous ectopic	27	(30)
? Spontaneous abortion	19	(21)
? Cyst	3	(3)
IUCD ?Pregnant	2	(2)
Back pain & PV bleeding	2	(2)
Other	6	(7)
Total	91	

Discussion

Pregnancy testing is a widely used service and is peculiar in that it is available from health care professionals, pharmacists and from supermarkets. The results from this study show that about seven pregnancy tests were performed for each live birth and about five for each proven pregnancy in the district in 1990. About 44 pregnancy tests were performed for every 100 women of childbearing age (15–44 years of age) during the year. If one assumes that the situation in the study district is similar to that elsewhere in England and Wales, the number of tests can be crudely extrapolated to 4.8 million pregnancy tests per annum in England and Wales.

The cost of pregnancy testing kits used by the health authority was 12.5 pence per test for the Pregnosticon Planotest® (low sensitivity haemagglutination) and 80 pence for the Hexagon® (high sensitivity ELISA) tests. The cost of performing a pregnancy test has been calculated using WelCan Units (Welsh Office 1989) which take account of staff costs, depreciation, heating, estate management, etc, and was £3.29 per test (average for both sorts of test, 3.45 WelCan units per test).

The approximate cost to the health authority was therefore about £13 000 for the year of 1990. This study found that 17% of tests were repeats within a 4 month period. If one arbitrarily assumes that half of these may have been unnecessary, £1100 could have been saved in this district if these tests had not been requested.

The cost of pregnancy tests sold over the counter in the study district in 1990 was about £50 000, and therefore the largest proportion of the cost of pregnancy testing in the district was borne by the women themselves. The need for counselling with pregnancy testing, especially in adolescents, has been discussed previously (Stephenson 1989) and there have been suggestions that pharmacists should be doing more to promote the appropriate use of testing kits (Coons 1989). The increasing sale of the tests by supermarkets will make this more difficult.

It is not known why so many pregnancy tests are performed. Many women may be very keen to be pregnant, while others with amenorrhoea for whatever reason may be seeking reassurance that they are not. The fact that more primiparous women had more than one pregnancy test during the pregnancy may reflect their heightened apprehension. That so many pregnancy tests are performed may suggest that family planning advice is lacking or does not leave women confident that they are unlikely to have conceived. Repeated testing by health care professionals is easy to criticise but, faced with an anxious patient, a pregnancy test may be a good method of reassurance.

A particular problem encountered during this study with self administered tests concerns their high sensitivity and the resulting ability to detect pregnancy earlier than routine hospital tests. This may produce the situation where a woman who has a positive home test does not trust this result and asks her doctor or the family planning clinic to confirm pregnancy. If it is still early in the pregnancy this second (lower sensitivity) test may return negative. This may confuse the woman, her doctor and the pharmacist. The doctor may then request a third test to finally confirm pregnancy. This is unsatisfactory and uneconomical for both the NHS and the woman.

Only 2.8% of women who booked for maternity services during this survey had their pregnancy diagnosed clinically with no immunological test and some of these presented late in the pregnancy. The reasons why it is so important to have definite confirmation of pregnancy were discussed in a recent study (Pye & Thomas 1990). These include being able to plan accordingly, health-related reasons involving the adoption of a more healthy lifestyle and employment or family commitments. There is an obvious reason for early confirmation in women who wish to have the pregnancy aborted or where abnormal pregnancy is suspected. An American study has shown the low reliability of patient history in excluding pregnancy (Ramoska *et al.* 1989).

There is little justification in providing pregnancy tests for women who present to a doctor with missed periods saying that they are trying to get pregnant and who have signs and symptoms of pregnancy. There seems to be a reluctance to accept the doctor's clinical opinion and one wonders if the training of doctors has taught them to trust a laboratory test more than their own clinical judgement? In these circumstances perhaps a woman should purchase her own kit if she feels a need to confirm the pregnancy. The results of this study suggest, however, that even when a self test is performed many women often desire a hospital test which may be perceived as more accurate. The request for a pregnancy test in women who are clinically pregnant seems unnecessary and is an example of the medicalisation of society (Ilich 1975).

Unless there are good medical reasons, women who want formal confirmation of pregnancy should be advised that the quickest way of achieving this is to purchase a self testing kit and they should be reassured that these tests, when performed correctly, are at least as sensitive as those performed in hospital.

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FERTILITY CONTROL

Induction of abortion with mifepristone and misoprostol in early pregnancy

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ABSTRACT

Objective To investigate the clinical efficacy of the combination of mifepristone and an orally active prostaglandin, misoprostol, for early medical termination.
Design Women with amenorrhoea ≤56 days were given 200 mg mifepristone. 48 h later, 600 µg misoprostol was given orally.
Setting Medical Termination Unit, Simpson Memorial Maternity Pavilion, Edinburgh.
Subjects 100 women requesting medical termination of pregnancy.
Interventions Evacuation of uterus for incomplete abortion or on-going pregnancies.
Results One woman had an incomplete abortion prior to administration of misoprostol. 92 (93%) out of 99 women had complete abortion following administration of misoprostol. There were three on-going pregnancies (3·0%, 95% confidence limits (CL) 0 6–8·6) and four incomplete abortions with this regimen (4·0%, 95% CL 1·1–10·0). 24% women vomited and 7% had diarrrhoea following administration of misoprostol. 62% did not require any analgesia.
Conclusions The combination of misoprostol with mifepristone is inexpensive, simple, effective, noninvasive and an acceptable alternative to current regimens for medical termination.

Medical termination of pregnancy using a combination of mifepristone and prostaglandin is a safe, effective alternative to vacuum termination up to the first 9 weeks of pregnancy (Sylvestre *et al.* 1990; UK Multicentre Trial 1990). The two most widely used prostaglandins, gemeprost and sulprostone, are administered as a vaginal pessary or by intramuscular injection, respectively. In practice, both routes of administration of prostaglandin are not ideal. These prostaglandins are expensive, require refrigeration before use and cardiovascular complications including a maternal death from myocardial infarction after administration of sulprostone have been reported (Kalra *et al.* 1989; Anonymous 1991).

An oral prostaglandin that could be used in combination with mifepristone for early medical termination may be more acceptable to women undergoing the procedure. The results of oral PGE_2 in combination with mifepristone was disappointing (Swahn *et al.* 1989) but a 95% complete abortion rate was achieved following administration of 9-methylene PGE_2 (Swahn *et al.* 1990). However, the fact that the latter was administered in solution would limit its use in clinical practice.

Misoprostol is a stable, orally active synthetic analogue of prostaglandin E_1 which is used for the prophylaxis and treatment of peptic ulcer. It is cheap, effective and associated with fewer gastrointestinal side effects (Herting & Nissen 1986). Misoprostol has a uterotonic effect and it is contraindicated for women in early pregnancy. 800 µg misoprostol when administered to pregnant women between 9–12 weeks gestation within 12 h of vacuum aspiration resulted in 11% partial or complete abortion (Rabe *et al.* 1987). 400 µg misoprostol administered 4 hourly to 20 women in the second and third trimester induced expulsion of the fetus in all of these women (Neto *et al.* 1988). We previously demonstrated that the uterotonic effect of misoprostol was markedly enhanced in women who had been treated 24–48 h previously with 200 mg mifepristone (Norman *et al.* 1991). Preliminary reports suggest that misoprostol in combination with mifepristone at a dose of 200 mg (Norman *et al.* 1991) or 600 mg (Aubeny & Baulieu 1991) may be as effective as gemeprost or sulprostone for inducing early abortion but with fewer side effects. In this study we report our experience in the use of misoprostol in combination with mifepristone for induction of abortion in 100 women in early pregnancy.

Subjects and methods

One hundred pregnant women (amenorrhoea ≤56 days) who were referred to the Edinburgh Royal Infirmary requesting a medical termination were recruited for this study. Informed consent was obtained from all women whose age ranged from 17–41 years. The gestational age was assessed by the menstrual history, pelvic examination and by pelvic ultrasound. Approval for the study was granted by the

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Table 1. Characteristics of the women.

Characteristics	Median	(range)
Age (yrs)	26	(17–41)
Height (cm)	164	(148–178)
Weight (kg)	60	(42–98)
Gestation (days)	50	(36–56)
Maximum diameter of sac (mm)	26	(9–52)
Parous	51	(51%)

Local Ethical Subcommittee. All of these women had grounds for termination of pregnancy under the 1967 Abortion Act.

Routine endocervical swabs for bacteriological culture, including chlamydia screening, were carried out. When a decision was made to terminate the pregnancy, arrangements were made for the women to come into hospital for the administration of mifepristone.

On the first day of treatment (day 1), blood was taken for estimation of haemoglobin concentration and blood group. A pelvic ultrasound scan was carried out. After receiving 200 mg mifepristone, the women returned home and were re-admitted 48 h (day 3) later for the oral administration of 600 µg of misoprostol. On day 3, the symptom questionnaire was completed before administration of misoprostol, and 2 and 4 h later. Blood pressure, pulse and temperature were measured hourly. Women who required analgesia were given paracetamol (1 g), dihydrocodeine (30 mg) or diamorphine (5 mg). Four hours following the administration of misoprostol, a vaginal examination was carried out to exclude excessive bleeding and to confirm whether the fetus had been expelled.

Anti-D was administered to rhesus negative women prior to discharge from hospital. A menstrual calendar was given to each of these women to record the number of days of bleeding and they were advised to use a barrier method of contraception until the next period. These women were followed up on day 8, 15 and 43 after the administration of the misoprostol or until the next menstrual period.

Statistical analyses were carried out using the χ^2 test, Mann–Whitney *U* test and the paired *t* test. Values were expressed as median (range).

Results

Table 1 shows the characteristics of the women.

An emergency curettage of the uterus was necessary on one woman admitted 48 h after administration of mifepristone because of heavy bleeding as a result of incomplete abortion. Of the remaining 99 women who were given misoprostol, 92 (93%) had complete abortion. There were three ongoing pregnancies which were terminated by vacuum aspiration. In addition, four women had incomplete abortions which required a curettage of the uterus.

Within 4 h of administration of misoprostol, all women had vaginal bleeding and 79% patients passed the fetus and/or placental tissue. There was no apparent difference in clinical efficacy in relation to gestation. There was one ongoing pregnancy and two incomplete abortions in 49 women with amenorrhoea of up to 49 days. The solitary woman with an ongoing pregnancy in this category was a 32 year old para 1+0 who was 38 days pregnant; vacuum aspiration was carried out 2 weeks later. In 50 women with pregnancies in the gestational age range of 50–56 days, there were two ongoing pregnancies and two incomplete abortions. With the exception of one woman, histological examination of the curettings confirmed residual trophoblastic material. In the whole group of 99 women the ongoing pregnancy rate was 3·0% (95% CL 0·6–8·6) and the incomplete abortion rate was 4·0% (95% CL 1·1–10).

Table 2. Analgesic requirements.

	n	(%)
None	61	(62)
Paracetamol only	21	(21)
Dihydrocodeine ± paracetamol	14	(14)
Diamorphine ± dihydrocodeine ± paracetamol	3	(3)

62% of women did not require any analgesia and only 3% women required diamorphine (Table 2). There was a significant decrease in nausea and breast tenderness following administration of misoprostol (Table 3). Over a 4 h period, there was a significant increase in vomiting, abdominal pain, faintness and diarrhoea. No significant change was noted in women for dizziness and none of the women in this study had hypotension. Complete abortion occurred in all women (24%) who vomited in the 4 h following swallowing misoprostol.

The median (range) body mass index of women who aborted successfully and women who did not were 21·8 (16·8–39·7) kg/m^2 and 22·4 (17·9–31·2) kg/m^2, respectively. The median (range) duration for bleeding was 14 (1–69) days. The mean interval from induction of abortion to menstruation was 37 (18–69) days.

There was a small but significant fall in the concentration of haemoglobin between day 1 and day 8 (12·6±0·08 versus 11·9±0·09 g/dl; *P*<0·0001). Three women were given intramuscular ergometrine (500 µg) for heavy bleeding at the time of expulsion of products. Two of these were anaemic (haemoglobin <10 g/dl) following abortion and required iron given orally; the haemoglobin (pretreatment) concentration of one woman dropped from 13·3 g/dl to 9·8 g/dl, and a drop from 12·1 g/dl to 9·7 g/dl was recorded in the other. Chlamydia was isolated from 3 (3%) asymptomatic women who were treated with oral doxycycline prior to administration of misoprostol. After abortion there was no clinical evidence of pelvic infection.

Table 3. Point prevalence of symptoms (before and following administration of misoprostol). NS = not significant.

Symptoms	0 h	2 h	4 h	Significance
Nausea	50	57	20	*P*<0·001
Vomiting	11	24	11	*P*<0·02
Fainting	39	59	39	*P*<0·01
Abdominal pain	11	85	78	*P*<0·001
Breast tenderness	37	31	19	*P*<0·02
Diarrhoea	1	7	1	*P*<0·02
Dizziness	16	24	15	ns

Discussion

This study demonstrates a 93% complete abortion rate when this regimen was used for the medical termination of pregnancy of up to 56 days amenorrhoea. The complete abortion rate was not influenced by gestational age or body mass index (Quetelet's index). A 95% complete abortion rate was obtained when 400 μg misoprostol was used in combination with 600 mg mifepristone for termination of pregnancies of up to 49 days amenorrhoea (Aubeny & Baulieu 1991). Although the gestational age, the dose of mifepristone and misoprostol were different in the two studies, the rates of complete abortion are similar.

The 3% incidence of ongoing pregnancies with this regimen is slightly higher than that reported using a combination of mifepristone with gemeprost or sulprostone (Sylvestre *et al.* 1990; UK Multicentre Trial, 1990). We have previously reported ongoing pregnancies in two out of 21 women (up to 56 days amenorrhoea) who were given 200 mg mifepristone followed by 200 μg and 400 μg of misoprostol (Norman *et al.* 1991). Therefore, in a consecutive series of 121 women treated with mifepristone and misoprostol in our centre, the ongoing pregnancy rate was 4% (95% CL 0·6–8·6%). In a consecutive series of 470 pregnancies (<56 days) terminated with mifepristone (50–600 mg) and gemeprost (0·5 mg–1 mg) in our institution, there has been only one ongoing pregnancy (0·2%). If the higher incidence of ongoing pregnancies is confirmed by a larger study (such as the one currently being conducted in France), the clinical usefulness of this combination of mifepristone and oral misoprostol for routine clinical use would be in doubt.

The increase in prostaglandin related side effects following administration of misoprostol (vomiting, pain, faintness and diarrhoea) was expected and the significant decrease in breast tenderness is probably related to a fall in hormonal levels following separation and expulsion of the conceptus. The fact that all women who vomited within 4 h of swallowing the misoprostol had a complete abortion, suggests that the absorption of misoprostol was unimpaired and the vomiting may reflect relatively higher levels of the compound in blood.

Although 85% women complained of abdominal pain within 4 h of taking misoprostol, pain was mild in the majority; opiate analgesia was requested by only 3%. This analgesic requirement was lower than when gemeprost was administered (UK Multicentre Trial 1990; Rodger *et al.* 1989). 62% did not require any form of analgesia and none of the patients were hypotensive following administration of misoprostol. This remains the main advantage with this regimen in terms of patient management. The incidence of vomiting following administration of misoprostol was similar to the administration of gemeprost, but the incidence of diarrhoea was lower with misoprostol (UK Multicentre Trial 1990).

79% women aborted within 4 h following administration of misoprostol. This is similar to a previous study (Aubeny & Baulieu 1991) and comparable to gemeprost. The duration of bleeding following abortion is similar to the regimen of mifepristone and gemeprost (Rodger *et al.* 1989). The interval to the next menses is slightly longer than the combination of mifepristone and gemeprost (Rodger *et al.* 1989; Norman *et al.* 1992). Although the potency of misoprostol is lower in comparison to gemeprost, this did not influence the duration of bleeding.

One woman in this study had an incomplete abortion following mifepristone prior to administration of misoprostol. Heavy bleeding due to incomplete abortion is a well recognised, albeit a rare complication, of mifepristone, and therefore women should have easy access to hospital should complications arise.

Compared to sulprostone or gemeprost, misoprostol is cheap, stable and does not require refrigeration. In addition, it is available worldwide with minimal risk of cardiovascular complications resulting from the dosage employed. 600 μg misoprostol costs £0.69 UK in contrast to 1 mg gemeprost which costs £21. In the present study we have further reduced the cost by employing 200 mg as compared to 600 mg of mifepristone. It was recently reported in a large multicentre trial supported by the World Health Organization that 200, 400 and 600 mg of mifepristone in combination with 1 mg gemeprost were all equally effective at inducing abortion (Maurice 1991). Further studies would be required to investigate whether a higher dose of mifepristone in combination with 600 μg misoprostol would increase the complete abortion rate.

In conclusion, misoprostol in combination with mifepristone is a safe, effective and relatively acceptable method of inducing abortion in early pregnancy. Larger trials will be required to determine whether this oral prostaglandin with its relatively low incidence of troublesome side effects can be used as an alternative to gemeprost or sulprostone without significant loss of clinical efficacy.

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REPRODUCTIVE SCIENCE

A prospective, randomised, cross-over study comparing the effects of clomiphene citrate and cyclofenil on endometrial morphology in the luteal phase of normal, fertile women

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ABSTRACT

Objective To examine the effect of two anti-oestrogens, clomiphene citrate and cyclofenil, on endometrial morphology in the luteal phase.

Design A prospective, randomised, cross-over study.

Setting Jessop Hospital for Women, Sheffield, UK.

Subjects 10 women who were previously fertile and regularly cycling.

Intervention The administration of clomiphene citrate or cyclofenil in the treatment cycles. A LH timed endometrial biopsy was taken on day LH + 6.

Main outcome measures Histological dating and morphometric analysis of the endometrial sample.

Results Only one out of 10 subjects had abnormal endometrium. There was no difference in the results between cycles treated with clomiphene citrate and cyclofenil.

Conclusions Clomiphene citrate or cyclofenil does not have a major adverse effect on endometrial morphology in the luteal phase of normal fertile subjects. The possible adverse effects of anti-oestrogens on endometrium may have been previously overestimated.

Clomiphene citrate has been widely used for over 20 years for the induction of ovulation. However, it is well recognised that the pregnancy rate achieved with clomiphene citrate is significantly lower than the ovulation rate (Wu 1984; Birkenfield *et al.* 1986; Scialli 1986). It has been postulated that such a discrepancy between ovulation and conception rates may be due to abnormal cervical mucus (Maxon *et al.* 1984), or abnormal endometrial development (Jones *et al.* 1970; Garcia *et al.* 1986; Scialli 1986) associated with treatment by clomiphene citrate. In a recent review, Birkenfield *et al.* (1986) commented that 'there is ample evidence that clomiphene may impair the endometrium and the process of implantation. The high incidence of luteal phase defect associated with the use of clomiphene reported by several clinics cannot be ignored.' On the other hand, it is unclear if other anti-oestrogens such as cyclofenil suffer from similar disadvantages.

We hypothesised that endometrial development in the luteal phase is less likely to be adversely affected by cyclofenil, a weaker anti-oestrogen, than clomiphene citrate. To test this hypothesis, we conducted a randomised, cross-over study to examine the effects of these two anti-oestrogens on endometrial thickness and endometrial morphology in a group of normal, fertile subjects.

This study has been approved by the local hospitals' ethics committee. Informed, written consent was obtained from each woman participating in the study.

Subjects and methods

A total of 10 normal, fertile volunteers were recruited from the Gynaecology Outpatient Clinic at the Jessop Hospital for Women, Sheffield to the study. All the women had to fulfil the following criteria: (a) aged between 20–40 years; (b) previously proven fertility; (c) regular cycles between 25–35 days; and (d) not known to have used any steroid hormone or intrauterine contraceptive device for 3 months prior to the study.

Administration of anti-oestrogens

Each woman recruited received clomiphene citrate in one study cycle and cyclofenil in another study cycle (cross-over design). The wash out period between these two study cycles

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was 1 month. Each subject was randomised by lottery to receive either clomiphene citrate or cyclofenil in the first treatment cycle. Clomiphene citrate was administered as a daily dose of 50 mg from days 2 to 6 (inclusive) of the cycle, whereas cyclofenil was administered as a daily dose of 400 mg from days 3 to 12 (inclusive) of the cycle.

Starting from day 9 of each cycle, daily morning urine specimens were collected for luteinizing hormone (LH) assay (Li *et al.* 1987) until a definite LH surge was identfied. On day LH + 6 (six days after the LH surge), a 10 ml blood sample was taken for oestradiol and progesterone assays, endometrial thickness was measured by transabdominal ultrasonography, and an endometrial biopsy was obtained for morphological study.

Progesterone assay was by non-extraction, solid phase radioimmunoassay (RIA) using I^{125} as a marker (Diagnostic Products Limited, Abingdon, Oxon, UK). The sensitivity of the assay was 0·16 nmol/l and the mean intra and inter assay coefficients of variation were 7·2% and 7·9%, respectively.

Oestradiol (E_2) assay was by non-extraction, solid phase radioimmunoassay (RIA) using I^{125} as a marker (Diagnostic Products Limited, Abingdon, Oxon, UK). The sensitivity of the assay was 29 pmol/l and the mean intra and inter assay coefficients of variation were 5·4% and 6·4%, respectively.

Ultrasonographic measurement of endometrial thickness was performed by a transabdominal real-time scanner (Combison 320, Kretztechnik, Zipf, Austria). The maximal thickness of the endometrium on longitudinal section was measured three times, and the mean value obtained was used for subsequent calculation. The ultrasonography was performed by one observer. The endometrium was measured from the echogenic interface of the junction of the endometrium and myometrium and the result therefore represents the two layers of endometrium.

Endometrial biopsies were obtained from outpatients using a Sharman's curette (Down Surgical Ltd, Sheffield, UK). A single endometrial specimen was obtained from the fundus and upper part of the body of the uterus. Each specimen was fixed immediately in 2% glutaraldehyde in cacodylate buffer (pH 7·4) for 4–6 h. It was then washed in buffer, dehydrated and embedded in JB-4 (Polysciences Inc, Warrington, Pennsylvania, USA), a plastic polymer. The specimen was sectioned at 2 µm, and the sections were stained with acid fuchsin and toluidine blue for examination by light microscopy.

All the endometrial biopsies were examined histologically by two different methods: the traditional dating criteria (Noyes *et al.* 1950) and morphometry, i.e. quantitative measurements, the details of which have previously been described (Li *et al.* 1988). To avoid bias, the two methods of analysis were carried out independently of each other. Six women from each group were selected at random for additional morphometry of the stromal tissue. Measurement of stromal cell nuclear diameter, axial ratio and the volume fraction of stromal nuclei to endometrium were made as previously described (Dockery *et al.* 1990). All biopsy specimens were coded, so that the observers did not know the clinical details of each specimen at the time of histological analysis.

Table 1. The age, parity, body weight, height and body mass index (body weight/height^2) of the 10 women participating in the randomised, cross-over study comparing the effects of two anti-oestrogens, clomiphene citrate and cyclofenil.

Characteristic	Median	Range
Age (year)	34·5	24–39
Parity	3	1–5
Body weight (kg)	70·5	58·5–95·0
Height (m)	1·62	1·50–1·66
Body mass index (kg/m^2)	26·4	21·4–36·2

The follicular phase was defined as from the onset of menstruation to the onset of the LH surge, inclusive. The luteal phase was defined as from the day after the LH surge to the day preceding the onset of the next menstruation. The lengths of the follicular and luteal phases were recorded (in days) in each study cycle.

The endometrial morphology from the cycles treated with anti-oestrogens was compared to that obtained from a separate group of normal fertile women who had not received any treatment (n = 14) (Li *et al.* 1988). This group of subjects was otherwise similar to those included in this study.

Statistical analysis of data utilised the Statistical Package for Social Science (SPSS-X), available within the IBM computer at the University of Sheffield. The Wilcoxon matched-pair test was used to compare the data between clomiphene citrate and cyclofenil treatment cycles within the same subject. In comparing treatment and control cycles, the Wilcoxon two-sample test was used.

Results

A total of 10 women completed the study. Their age, parity, body weight, height and body mass index (body weight/height^2) are shown in Table 1. Five received clomiphene citrate in the first treatment cycle, whereas the other five subjects received cyclofenil in the first treatment cycle.

The observations of the cycles treated with clomiphene cit-

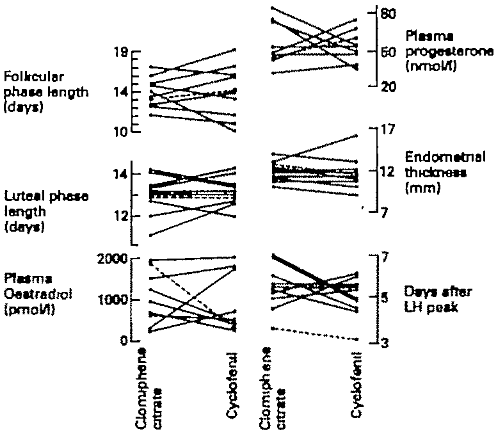
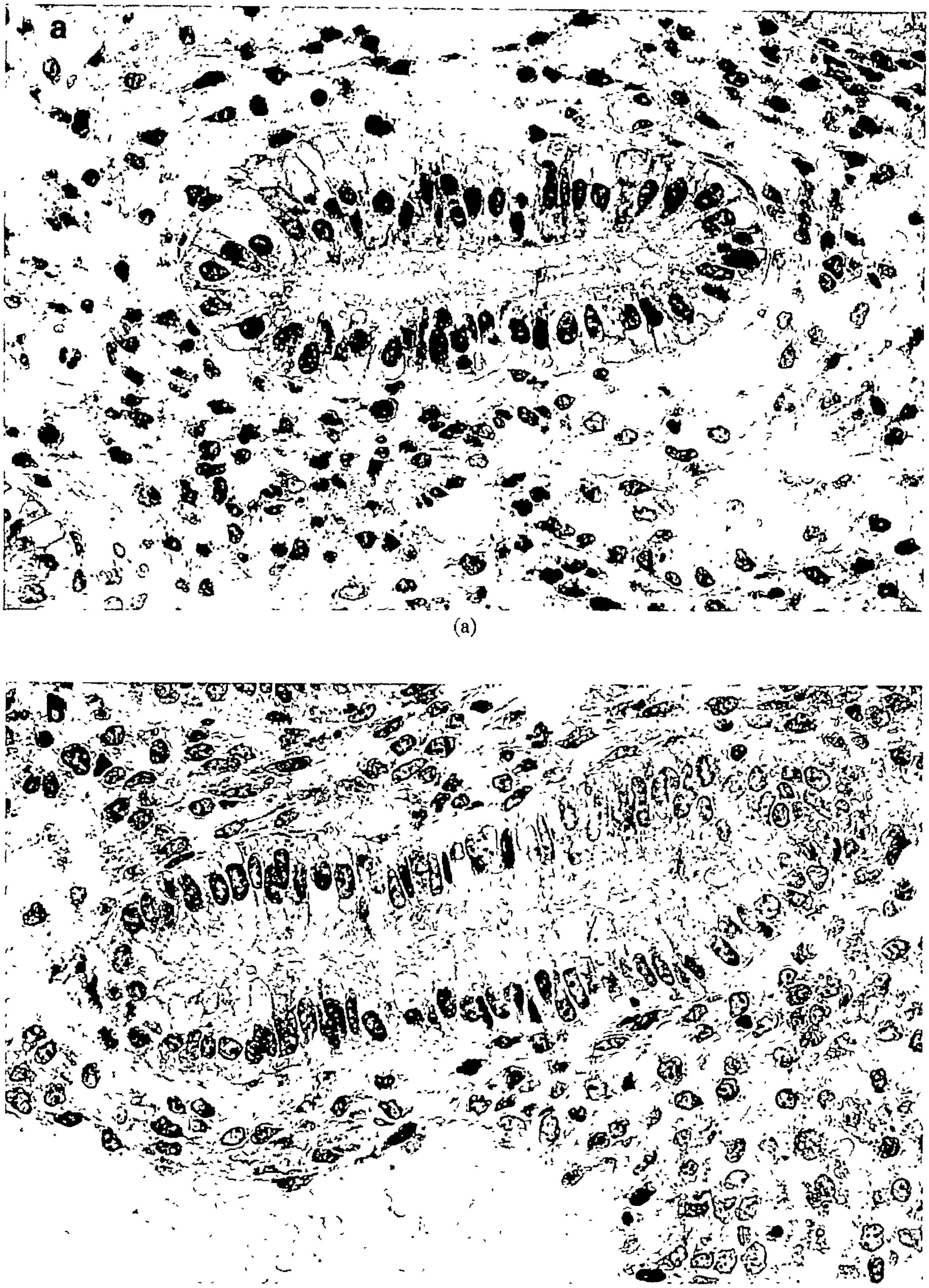


Fig. 1. A comparison of features between cycles treated with clomiphene citrate and cyclofenil in a prospective, randomised, cross-over study in 10 normal fertile women. Statistical analysis was carried out by using Wilcoxon matched-pair test; none of the features were significantly different between the two treatment groups. The histological dating was based on the traditional criteria of Noyes *et al.* (1950). The dotted line represents the woman whose endometrial responses to both clomiphene citrate and cyclofenil were abnormal.



(a)

(b)

Fig. 2. Typical examples of endometrial morphology on day LH + 6 following treatment with an anti-oestrogen in the follicular phase of the same cycle. (a) treatment with cyclofenil and (b) treatment with clomiphene citrate. Note the presence of a plentiful amount of secretory vacuoles within the gland cells and that secretory materials are just beginning to appear in the gland lumen Magnifications = ×500 for both (a) and (b)

rate are compared to those treated with cyclofenil. There were no significant differences between the two groups in the length of the follicular and luteal phases, plasma oestradiol and progesterone concentrations, endometrial thickness, and histological-dating results by the standard criteria of Noyes *et al.* (1950) (Fig. 1). In one woman, the plasma sample from the clomiphene citrate treated cycle was lost, so only nine pairs of endocrine data are shown in Fig. 1. In this woman, endometrial development was normal in both treatment cycles. Typical examples of endometrial morphology following treatment with clomiphene citrate and cyclofenil are shown in Fig. 2.

The histological dating was considered to be normal (within 2 days of chronological dating, i.e. LH + 4 –LH + 8) in nine out of 10 women in each treatment group. The woman with retarded endometrial development in the cycle treated with clomiphene citrate (LH + 3·5) was also the one who had retarded endometrial development in the cycle treated with cyclofenil (LH + 3). After the completion of the study, this woman had a further cycle studied without any anti-oestrogen treatment. The endometrial sample obtained on day LH + 6 of this cycle revealed histological development consistent with day LH + 5, i.e. normal.

The results of further histological analysis of the endometrial specimens by quantitative histological techniques (morphometry) are shown in Tables 2 and 3. There was no significant difference in results: between cycles treated with clomiphene citrate or cyclofenil; between cycles treated with clomiphene citrate and untreated cycles; and between cycles treated with cyclofenil and untreated cycles.

Discussion

In this prospective study, the effects of two anti-oestrogens, clomiphene citrate and cyclofenil on the luteal phase of normal, fertile women were examined and compared. Normal fertile, rather than infertile, women, were studied because the latter may have anovulation, or abnormal endometrial development in the luteal phase (Li *et al.* 1990). Any abnormality observed in the luteal phase of infertile women receiving anti-oestrogens may be associated with pre-existing underlying abnormality, or the effects of anti-oestrogens, or both. In contrast, any abnormality observed in normal fertile women receiving anti-oestrogens is more likely to be a result of the treatment.

Several problems are often encountered in any study attempting to examine endometrial morphology in the luteal phase (for review see Li *et al.* 1991). Two important, potential sources of errors are the timing of endometrial samples (chronological dating) and the accuracy of the histological assessment of the specimens (histological dating). In this study, we have reduced these errors by: timing of endometrial samples precisely in relation to the LH surge; having only one experienced observer to examine the morphology of the endometrium, thereby eliminating errors due to interobserver variability; and the application of established quantitative histological techniques, i.e. morphometry, which is both objective and reproducible (Li *et al.* 1988), to study the endometrium.

All the endometrial samples were obtained on day LH + 6. We chose this particular time because this is when embryos normally have just arrived in the endometrial cavity (Croxatto *et al.* 1978) and the process of implantation would be initiated at or shortly after this time (Hertig *et al.* 1956). We believe that the study of endometrial morphology at this time is more relevant than that of the late luteal phase when degenerative changes dominate the endometrial morphology.

Table 2. A comparison of some morphological features of endometrial samples obtained on day LH + 6 between cycles untreated or treated with anti-oestrogens. The cycles are compared by the Wilcoxon two-sample test (untreated vs clomiphene citrate, or untreated vs cyclofenil) and by Wilcoxon matched-pair test (clomiphene citrate vs cyclofenil). No significant differences were observed between the groups. The results shown are medians, with ranges in brackets.

Morphological features	Untreated cycles (*n* = 14)	Cycles treated with clomiphene citrate (cc) (*n* = 10)	Cycles treated with cyclofenil (cy) (*n* = 10)	Subject with abnormal response to anti-oestrogen	
				Clomiphene	Cyclofenil
Histological dating (day LH +)	6·0 (4·5–8·0)	5·5 (3·5–7·0)	5·3 (3·0–6·0)	3·5	3·0
Glandular mitosis (per 1000 cells)	0 (0–4)	0 (0)	0 (0–8)	0	8
Stromal mitosis (per 1000 cells)	0 (0–6)	0 (0–1)	0 (0–2)	0	1
Subnuclear vacuoles (per 100 gland cells)	12 (0–58)	22 (0–92)	28 (0–94)	63	26
Supranuclear vacuoles (per 100 gland cells)	5 (1–28)	11 (0–44)	8 (0–25)	8	0
Volume fraction gland cell/gland (%)	84 (73–93)	81 (71–93)	82 (70–94)	81	94
Volume fraction gland/stroma (%)	29 (20–34)	22 (15–27)	26 (13–37)	15	13

Table 3. Stromal cell dimensions and volume fraction data for each of the three study groups. Results are given as means and as standard errors in brackets.

Features	Untreated cycles ($n = 6$)	Cycles treated with clomiphene citrate ($n = 6$)	Cycles treated with cyclofenil ($n = 6$)
Volume fraction of stromal nucleus to endometrium (%)	16·8 (1·4)	16·2 (1·6)	14.6 (1·4)
Mean stromal nuclear diameter (μm)	5·2 (0·2)	4·9 (0·2)	5·2 (0·1)
Axial ratio of stromal nuclei	1·8 (0·2)	1·7 (0·1)	1·7 (0·04)

The finding in this study that there was no significant difference in plasma P concentration and endometrial morphology in the luteal phase of cycles treated with clomiphene citrate and cyclofenil suggests that there is unlikely to be any major difference in the effect of the two drugs on the physiological function of the endometrium at the time of implantation.

The observation that all cycles ($n = 20$) treated with anti-oestrogens developed an LH surge had a plasma progesterone concentration of at least 30 nmol/l on day LH + 6, and had evidence of secretory transformation in endometrial biopsy samples indicated that ovulation had occurred in all these cycles. It seems unlikely that anti-oestrogens adversely affect ovulation in women who are regularly ovulating.

In addition, the results of histological dating based on the standard criteria (Noyes *et al.* 1950) were within 2 days of the chronological dating and were considered to be normal in 90% of the women in each treatment group (Fig. 1). Although the number of women and cycles studied was relatively small, these observations indicated that anti-oestrogens do not have a major adverse effect on endometrial development. This is in contrast to the finding of a number of previous investigations (Jones *et al.* 1970; Garcia *et al.* 1977; Balasch *et al.* 1983; Cook *et al.* 1984; Wu 1984; Birkenfield *et al.* 1986; Scialli 1986) that the use of clomiphene citrate was associated with endometrial abnormality in a significant proportion. However, in all these previous studies, the women were infertile, with ovulatory disorders, whereas in this study they were normally fertile. It seems likely that the association previously observed between clomiphene citrate and endometrial abnormality in infertile women is more likely to be a consequence of underlying endocrine or endometrial abnormalities than to a direct effect of clomiphene citrate itself.

The woman who had retarded endometrial development in response to clomiphene citrate (histological dating LH + 3·5) also had similar, retarded endometrial response to cyclofenil (histological dating LH + 3). However, a subsequent cycle without any treatment revealed normal histological development. This indicates that in this particular woman the administration of an anti-oestrogen (whether clomiphene citrate or cyclofenil) had resulted in retarded development of the endometrium.

It is of interest to analyse the endocrinological and morphological features of the endometrium in the woman with abnormal endometrial development in response to clomiphene citrate and cyclofenil. While the endocrinological data was similar to those with normal endometrial development, morphometric analysis of the endometrium suggested that the volume fraction of gland/stroma was the lowest in the group on each of the two occasions (Table 2)—15% in response to clomiphene citrate and 13% in response to cyclofenil, as compared to a median of 22% and 26%, respectively. The data suggest either an increase in the absolute volume of the stromal componment or a decrease in the absolute volume of the glandular component of the endometrium. Our further observation that secretory material within the gland lumen was absent or minimal in these two samples supports the argument that the effect of the anti-oestrogen is more likely to be on the glandular rather than the stromal component. Another interesting feature is the increased number of glandular mitosis observed in the cycle treated with cyclofenil (8/1000), a value that is consistent with endometrial development around day LH + 2 to LH + 3, again suggestive of a direct effect of anti-oestrogen on glandular development.

Conclusion

We have found no major difference in endometrial morphology in the luteal phase between those treated with clomiphene citrate and cyclofenil, and between those who were treated with anti-oestrogens and those who were not. The latter suggests that previous research has overestimated the possible adverse effects of anti-oestrogens on endometrium.

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CASE REPORTS

Management of haemorrhage in a case of acute fatty liver of pregnancy by internal iliac artery embolisation

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Case report

A primigravid 42-year-old Filipino woman was admitted at 32 weeks gestation in preterm labour. Her pregnancy had been uneventful and she had no significant previous medical or surgical history. On arrival she was jaundiced, her blood pressure was 150/90 mmHg and there was no proteinuria. She was contracting regularly and her cervix was 3 cm dilated and fully effaced.

Laboratory investigations revealed disseminated intravascular coagulation (DIC) with an activated partial thrombin time with kaolin of 67 control 30, prothrombin ratio 32 control 13, fibrinogen 0·5 g/l and fibrin degradation products 80–160 µg/ml. Her renal function was impaired with urea of 5·7 mmol/l and creatinine of 0·21 mmol/l. Liver function tests revealed an aspartate transaminase of 105U/l, gamma glutamyl transferase 160 u/l and aspartate transminase 73 u/l with an alkaline phosphatose of 1192 u/l and a total bilirubin of 144 µmol/ml. Hepatitis B surface antigen and anti-hepatitis A virus IgM later proved negative and an ultrasound scan performed the following day showed a shrunken liver, ascites and no gallstones or dilated bile ducts.

She was transfused with 2 units of fresh frozen plasma whilst in labour because of her coagulopathy. She progressed rapidly to full cervical dilatation and a forceps delivery was performed because of fetal distress. A live male infant weighing 1·8 kg with Apgar scores of 6 and 8 at one and five minutes was born. The third stage of labour was managed actively and the episiotomy and vaginal lacerations were repaired. However, despite a firm uterine fundus, she had an immediate post partum haemorrhage of 1500 ml. Blood loss continued and she was transfused with 3 units of whole blood and 4 units of fresh frozen plasma following which her loss became minimal. She was transferred to the intensive care unit. Her coagulopathy persisted despite multiple further transfusions of fresh frozen plasma and fresh whole blood and vitamin K by injection.

The following day blood loss per vaginum increased, necessitating examination under anaesthesia and evacuation of clot from inside the uterine cavity. Consideration was given to performing a hysterectomy and internal iliac artery ligation, but, in view of her coagulopathy, this was thought too dangerous. A radiologist experienced in angiography was contacted and agreed to perform pelvic arteriography and emolisation of the bleeding vessels.

The arteriography was performed under local anaesthesia through a left femoral artery puncture. Bleeding was identified from branches of the right internal iliac artery (Fig. 1) and right internal iliac artery was embolised, using multiple gelfoam emboli. A post-embolisation angiogram confirmed that bleeding had stopped. Pressure was applied to the femoral artery puncture site and the patient was returned to the intensive care unit.

However, later that night, vaginal bleeding recurred. Arteriography was repeated and the right circumflex femoral and the right inferior epigastric arteries were embolised. Following this, blood loss was minimal overnight but, the following day, increased, necessitating a third procedure. Embolisation of the left internal iliac artery was performed (Fig 2). No further bleeding occurred.

The patient remained in the intensive care unit for a further four days during which time her jaundice improved, her ascites diminished and her coagulation studies and renal function slowly returned to normal. She was returned home 30 days after admission and three months later had recovered completely and her liver function had returned to normal. A diagnosis of acute fatty liver of pregnancy was made on clinical grounds alone, as liver biopsy was precluded in view of the coagulopathy.

Discussion

Acute fatty liver pregnancy was first described in 1934 (Stander & Cadder 1934); however, it was Sheehan (1940) who distinguished the condition from fulminant viral hepatitis. It has generally been regarded as a rare condition with a reported incidence of 1:13 320 deliveries (Polkros *et al.* 1984) and as having a high maternal mortality (85%) (Hatfield *et al.* 1972) and perinatal mortality (50%) (Fagen & Chadwick 1984). However, recent reviews have suggested a wider clinico-pathological spectrum with a more commonly occurring, less severe form of the disease (Bernucu *et al.* 1983; Kaplan 1985).

Disseminated intravascular coagulation has been widely reported in association with acute fatty liver of pregnancy (Polkros *et al.* 1984; Hatfield *et al.* 1972; Fagen & Chadwick 1984, Kaplan 1985; Caro *et al.* 1975; Liebman *et al.* 1983). It has been associated with maternal mortality (Hatfield *et al.*

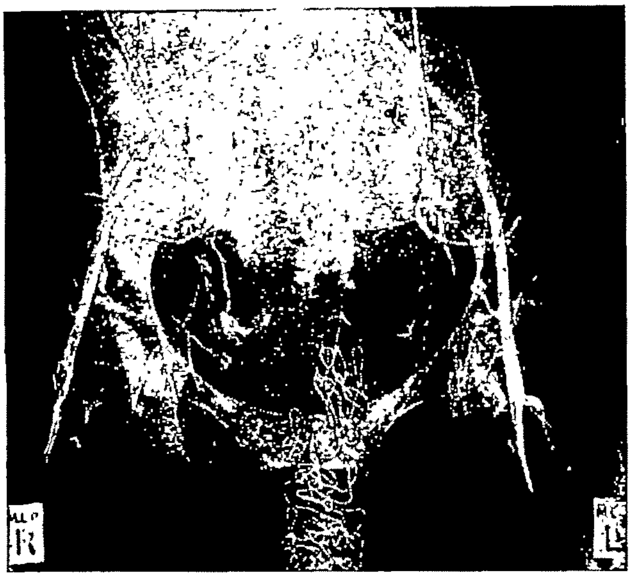

Fig. 1. Angiogram showing haemorrhage from branches of the right internal iliac artery.

1972), gastro-intestinal tract bleeding (Holzbach 1974; Caro *et al.* 1975), with hysterectomy and internal iliac artery ligation having been used to control haemorrhage (Liebman *et al.* 1983).

Unlike other obstetric causes of coagulopathy which usually improve soon after delivery, the process associated with acute fatty liver may take several days to resolve. It has been hypothesised that this is due to markedly reduced levels of antithrombin III (Liebman *et al.* 1983). The liver is responsible for metabolizing fibrin degradation products and this may be another reason for the prolongation of the coagulation defect associated with acute fatty liver of pregnancy (Boulton & Letsky 1985; Pritchard *et al.* 1985).

Hysterectomy may be necessary in the management of otherwise uncontrollable uterine haemorrhage (Holzbach 1974). However, if there is coagulopathy, surgery may intensify the haemorrhage. Hysterectomy and internal iliac artery ligation for the control of haemorrhage in a patient with coagulopathy secondary to acute fatty liver of pregnancy with successful outcome has been reported (Liebman *et al.* 1983). In our case, hysterectomy was avoided by the use of internal iliac artery embolisation.

It is interesting that bilateral ligation of the internal iliac arteries, per se, does not appear to interfere seriously with subsequent reproduction (Pritchard *et al.* 1985) and pregnancy following bilateral internal iliac artery embolization has occurred (Dr W. Sorby, personal communication).

Angiographically-controlled selective embolisation techniques have become an increasingly popular method of treating acute haemorrhage. They have been widely used to control bleeding from duodenal ulcers, oesophageal variies and with renal haemorrhage. Gelfoam is the most widely used agent for achieving vessel embolisation. The occlusion produced by gelfoam is not permanent, and most vessels recanalise within ten days to several weeks (Ring & McLean 1981). Following gelfoam embolisation patients commonly develop a fever up to 38·5°C, which may persist for 24–36 h (Ring & McLean 1981).

Recurrent bleeding from a collateral circulation is a problem with angiographic vessel embolisation. After a vessel has been occluded in an area rich with potential collaterals, it is important to demonstrate the alternatve blood supplies to ensure that haemostasis has been achieved. If repeat angiography shows continued extravasation through a collateral branch, further therapy is warranted. In the case presented here, post embolisation angiograms did not show any immediate haemorrhage from the collateral circulation, but this developed at a later stage.

Inadvertent reflux of the embolic material into areas sensitive to ischaemic infarction is one of the greatest hazards of embolic therapy (Ring & McLean 1981). By cautious injection of the emboli with contrast medium and close fluoroscopic monitoring of the progress of the embolisation, complications can be prevented.

The use of embolisation techniques to control bleeding from branches of the internal iliac arteries has been described (Ring & McLean 1981). Experience has shown that any or all branches of this vessel can be safely occluded. On rare occasions, the sciatic nerve undergoes ischaemic damage, but generally internal iliac artery embolisation is considered a safe procedure. However, angiographic identification of, and embolic occlusion of, pelvic or other bleeding sites depends on the 24 h availability of experienced angiographic radiologists. Where such skills are not available, surgical ligation may be necessary because inexperienced angiographic embolisation can result in serious complications.

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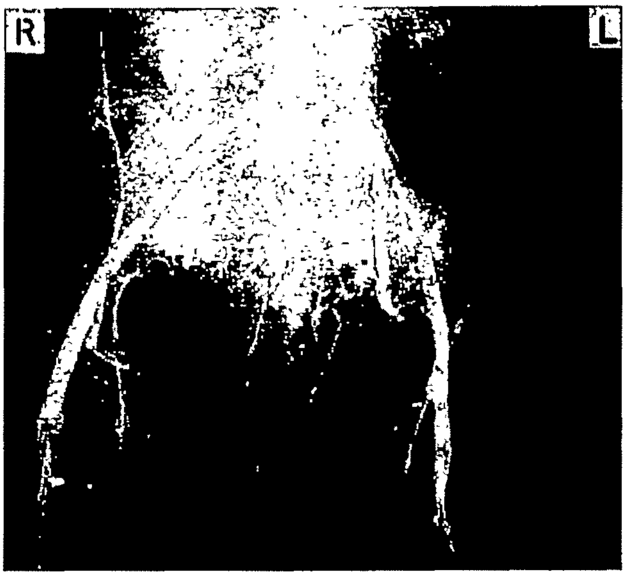

Fig. 2. Angiogram following gelfoam embolisation of the left internal iliac artery, the right circumflex femoral and the right inferior epigastric artery.

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Selective IgA deficiency combined with immune thrombocytopenic purpura in pregnancy—problems in management

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Case report

A 31-year-old woman was referred to the High Risk Pregnancy Unit in the 32nd week of her seventh pregnancy. Until then she had been treated by the haematology service. Idiopathic thrombocytopenic purpura (ITP) had been diagnosed by bone marrow biopsy and peripheral smear one year prior to her referral. The patient was known to have a total lack of IgA, as demonstrated by studies of immunoglobulins in blood and saliva, and by plasma electrophoresis.

Correspondence. Dr M. Hod.

On admission the patient was generally well and was normal on physical examination. There was no sign of subcutaneous or submucosal bleeding. Relevant laboratory findings were: haemoglobin concentration 10·8 g/dl; white cell count 9900/ µl, platelet count 46 000/µl. Coagulation studies, liver and renal function tests and routine blood chemistry were all normal. No circulating anticoagulant was detected. Plasma was positive for antinuclear factor to a titre of 1:160, but negative for anti-double stranded DNA.

Treatment with prednisone 40 mg per day, which had been started at 22nd week of gestation because of a platelet count of 40 000/µl. was continued.

During her stay in hospital, the platelet count decreased further to a level of 35 000/µl. As intravenous gammaglobulin could not be administered because of the IgA deficiency, the prednisone dose was increased to 60 mg per day, but this failed to increase the platelet count above 43 000/µl.

Uterine contractions began at 33 weeks' gestation. Intravenous ritodrine therapy was begun but, despite maximal doses, labour progressed. In order to decide on the safest route of delivery, a percutaneous umbilical fetal blood sampling was obtained. The umbilical blood obtained had a platelet count of 40 000/µl and an MCV of 110 fl. Because labour was progressing and because of the degree of fetal thrombocytopenia, a caesarean section was performed. Prior to the section, the maternal platelet count was 30 000/µl but platelet transfusion was not possible because of the IgA deficiency. During the operation an umbilical cord blood sample was obtained, showing a platelet count of 38 000/µl. The operative and post-operative course was entirely uneventful. Twenty-four hours after birth the baby's platelet count increased to 100 000/μl, and the mother's to 110 000/μl.

Discussion

A small number of women of childbearing age encounter problems related to the immune system, usually immunodeficiency or autoimmunity and, in rare cases, both. Selective IgA deficiency is the most common immunodeficiency disorder with a prevalence of 1:400 to 1:800 (Ammann & Hong 1971). The basic defect in IgA deficiency has not been defined. If women who completely lack IgA receive IgA from any source, the immune system responds to it as a foreign substance and an anti-IgA response and anaphylaxis may occur (Vyas *et al.* 1968). Thus, neither gammaglobulins nor blood products may be transfused because of the high risk of acute severe anaphylactoid, immune-complex mediated reactions.

Immune thrombocytopenic purpura (ITP) occurs quite frequently in young women during the reproductive age and may be first diagnosed by the obstetrician. Platelet reactive autoantibodies, commonly IgG, may cross the placenta and causes fetal and neonatal thrombocytopenia. The cornerstone of the treatment of ITP is the use of steroids, administered either alone or in combination with intravenous high dose gammaglobulins and, in very rare severe cases, platelet transfusion prior to caesarean section (Martin *et al.* 1984; Scott 1990). However, in a patient with complete lack of IgA, intravenous gammaglobulins cannot be given for fear of the acute reaction described above. Similarly, the transfusion of any blood product, including platelets or packed red blood cells, carries a risk of the same reaction.

In fetal medicine, it is important to mention the possibility of treating the fetus of the woman suffering from ITP by giving immunoglobin by cordocentesis or into the fetal hepatic vein in order to achieve an increase in fetal platelet count. The possibility of maternal IgG antibody in the fetus causing an anaphylactoid reaction, however, would be a contraindication to such an approach.

Reports describing low levels of IgA or even a complete lack of it in non-pregnant patients with ITP, have been published (Khalifa *et al.* 1976; el-Khateeb *et al.* 1986) but, to the best of our knowledge, this is the first published description of the combination in pregnancy of ITP and selective IgA deficiency. This report demonstrates the difficulties involved in the management of such a patient.

The diagnosis of fetal thrombocytopenia and assessment of the effects of treatment is best achieved by the performance of umbilical blood sampling. If the fetus is indeed found to be thrombocytopenic (platelet count below 50 000/μl), the tendency is to deliver by caesarean section. This approach might avoid the possibility of intracranial bleeding that might occur during a vaginal delivery (Samuels *et al.* 1990).

Thus selective IgA deficiency complicates the management of the pregnant woman with ITP in two ways: firstly, the use of intravenous gammaglobulins is impossible, and secondly, the use of other blood products is severely restricted, even though there is a high likelihood of a caesarean section because of fetal thrombocytopenia.

The problem of transfusing blood products may be partially overcome by administering units of red blood cells or platelet donated by the patient herself before she becomes pregnant. Another possibility is to obtain red blood cells, platelet or other blood products from IgA deficient donors. Such units of blood products can be kept until required for up to 7–10 years (Meryman 1979; Walker 1990).

Patients with selective IgA deficiency show a large spectrum of associated clinical disorder, such as allergic problems, asthma, gastrointestinal dysfunction, pulmonary infections and autoimmune disorders such as rheumatoid arthritis (Levy & Douglas 1985). Those who become pregnant do not manifest particular abnormalities other than those described above. Most of these women are asymptomatic and do not require special therapy. Those with allergic, gastrointestinal or autoimmune disorder should be treated accordingly and precaution taken with regard to the medications that can provoke an acute anaphylactoid reaction. All IgA deficient patients should be warned of the risk of severe transfusion reaction which may occur following infusion of only few millimetres of blood.

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Endoscopic management of uterine perforation occurring during endometrial resection

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Case report

A 31-year-old healthy, multiparous woman underwent transcervical resection of the endometrium (TCRE) for dysfunctional uterine bleeding unresponsive to medical therapy. At operation the uterine cavity was noted to be normal but with a thickened endometrium which had not been medically thinned prior to surgery. Endometrial resection was started at the uterine fundus, but within minutes a sudden loss of uterine distension occurred with loss of visibility whilst resecting the right cornual region. It was simultaneously noted that 950 ml of the uterine irrigant, 1·5% glycine solution tagged with 1% ethanol (Baxter Healthcare Ltd, UK), had been absorbed by the patient, and the blood alcohol level was noted to be high at 40 mg/dl as assessed with a breath Alcolmeter (Lion Laboratories, UK). All these findings suggested the possibility of uterine perforation with rapid absorption of the irrigant. Hysteroscopic surgery was stopped immediately and the patient prepared for laparoscopy.

Laparoscopy confirmed a uterine perforation, medial to the insertion of the right fallopian tube, which was bleeding slightly. There was no other obvious trauma. Using two atraumatic grasping forceps inserted suprapubically, the rectum, sigmoid colon and ileum were systematically examined for evidence of burns or perforation but no visceral damage was noted. The uterine perforation was stitched laparoscopically using endosutures (Ethicon, Germany). This achieved satisfactory haemostasis but uterine distension was not possible due to continued leakage of irrigant from this site. The perforation was therefore 'plugged' hysteroscopically with a chip of resected endometrium to allow sufficient distension to complete the endometrial resection. Total fluid absorption was 1650 ml by the end of surgery. Postoperatively, vital signs remained normal and the patient was discharged from hospital 48 hours later. Antibiotics were continued for one week.

Discussion

TCRE is becoming increasingly widely performed in the United Kingdom; a recent audit by the Royal College of Obstetricians found that 47% of acute units are now offering this procedure to patients with menorrhagia (RCOG Audit 1991). In accordance with our own experience (Magos *et al.* 1991), this survey confirmed that the procedure is safe with serious complications such as uterine perforation and fluid overload being relatively uncommon.

However rare uterine perforation during endometrial resection may be, it is an important operative complication; once recognised surgery has either to be abandoned to prevent excessive intraperitoneal loss of uterine irrigant or to be continued only after laparotomy to check for intra-abdominal trauma and allow uterine repair, that is, a choice between incomplete treatment or major open surgery. Here we have described a third option whereby purely endoscopic techniques are utilised: laparoscopic assessment of the perforation and intra-abdominal contents, laparoscopic repair of the uterus, hysteroscopic plugging of the myometrial defect to affect a fluid-tight seal allowing completion of the resection under laparoscopic control whilst avoiding laparotomy.

This case demonstrates that in the absence of major intra-abdominal trauma endometrial ablation can be continued successfully even after uterine perforation without resort to laparotomy or hysterectomy. It also illustrates the value of using ethanol labelled glycine solution and measuring breath ethanol concentrations during surgery, not only as an aid to the estimation of overall fluid absorption (Molnár *et al.* 1992) but also as a rapid warning system against possible uterine perforation.

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Luteoma of pregnancy: masculinisation of a female fetus prevented by placental aromatisation

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Case report

Miss C. E., an 18 year old woman, had been diagnosed previously at age 16 as having non-insulin dependent diabetes mellitus and treated thereafter with diet and metformin. At the time of her original diagnosis, she had been overweight (95 kg) with oligomenorrhoea and slight hirsutism with a serum testosterone concentration of 3·6 nmol/l. Cushing's disease was suspected, but both measurements of diurnal cortisol and a dexamethasone suppression test proved normal.

She then presented 2 years later with elevated plasma glucose recordings and 2% glycosuria; at that time she was found to be 8 weeks pregnant, was admitted and insulin was commenced. At 16 weeks she developed marked hirsutism with voice deepening but no temporal hair recession. The serum testosterone concentration was 25·7 nmol/l (Table 1). Details of all other antenatal steroid measurements are shown in Table 1. Ultrasound examination of both ovaries and the adrenal gland revealed no significant abnormality or enlargement. During the remainder of the pregnancy , she gradually developed frontal recession and marked clitoromegaly. Her insulin requirements increased steadily to a total of 43 units by delivery.

At 25 weeks she was admitted with marked mucoid vaginal discharge and pelvic heaviness. On clinical and ultrasound examination, the cervix was found to be very short and gaping. In view of this, a cervical suture was inserted. At 29 weeks, she was readmitted with ruptured membranes and the suture was removed. She was then delivered by caesarean section at 31 weeks due to an intermittent pyrexia and a rising white cell count. A healthy girl was born weighing 1·935 kg with entirely normal external genitalia and no evidence of masculinisation. Samples were obtained at operation for testosterone estimation before induction of anaesthesia (peripheral sample 1) and, during the operation, from a peripheral vein (peripheral sample 2), from the right ovarian vein and the umbilical artery. The results are shown in Table 1. The ovaries were found at operation to be solid with no evidence of either cyst formation or a discrete tumour. Measurement of the ovarian size at operation, using cut sutures which were then measured with a ruler, revealed only moderate ovarian enlargement (right, 5;3 × 3·1 × 2·5 cm; left, 4·1 × 3·2 × 2·3 cm). A wedge biopsy of the right ovary was performed. The histological appearances were those of a luteoma of pregnancy with large numbers of Leydig cells present and no evidence of malignancy.

Following delivery, her serum testosterone concentrations fell rapidly and by 2 months after delivery the level was considerably lower than that prior to the pregnancy at 1·9 nmol/l. An ultrasound scan of her pelvis revealed no abnormality. Her hirsutism, voice changes and clitoromegaly, however, persisted.

Discussion

Luteoma of pregnancy is an uncommon condition characterised by non-neoplastic swellings of the ovary which regress following delivery (Garcia-Bunuel *et al.* 1975). In many cases, as here, the woman experiences considerable hirsutism or even virilisation. There are less than 200 cases documented in the world literature and only a small number of these reports describe the endocrine changes underlying this condition. Here we describe one such case in association with serial measurements of hormone concentration. From these measurements the following conclusions can be drawn:

(1) The testosterone arises from an ovarian source as the concentration of di-hydroepiandrosterone-sulphate, a steroid of exclusively adrenal origin, is unchanged. The concentration of testosterone in the ovarian vein sample obtained at delivery was greater than 127 nmol/l thus conclusively indicating a pelvic source, most probably ovarian, for the abnormal concentrations of circulating androgens.

(2) The hormone concentrations reverted to normal very rapidly following delivery, indicating dependence of the tumours on the endocrine effects of pregnancy, presumably hCG (Cohen *et al.* 1982). Indeed, the very low testosterone concentration seen at 6 weeks after delivery probably reflects continuing post partum suppression of the hypothalamic-pituitary-ovarian tract as the slightly high testerone concentration seen prior to pregnancy in this woman suggests the likelihood of pre-existing polycystic ovary syndrome.

(3) This condition does not arise as a result of abnormally high hCG concentrations.

Table 1. Hormone concentrations throughout gestation.

Gestation	hCG (u/l)	Testosterone (nmol/l)	Androstenedione (nmol/l)	Other
Pre-pregnancy		3·6		
11 weeks	68 906	11·9		
16 weeks		25·7	30·5	DHAS 3 6 µmol/l Cortisol 430 nmol/l
20 weeks		25·1	21·0	DHAS 3 3 µmol/l
23 weeks				17 OH Progesterone
26 weeks		17·7	27·5	
Delivery	32 403	20 —Peripheral sample 1		
31 weeks		26·1—Peripheral sample 2		
		>127 —Right ovarian sample		
		1·2—Umbilical vein sample		
5 days after delivery		4·6		DHAS 3·2 µmol/l LH 1·5 u/l FSH <0·7 u/l Oestradiol 87 pmol/l
9 days after delivery		3·4		DHAS 3·8 µmol/l LH <0·7 u/l FSH 2·1 u/l Oestradiol 70 pmol/l
6 weeks after delivery		1·6		

(4) The degree of abnormality of hormone secretion bears little relation to the size of the tumour. In this case there was a marked abnormality in circulating androgen concentration despite the presence of a solid tumour with only a moderate degree of ovarian enlargement.

(5) The cord blood testosterone concentration was entirely normal, indicating that the female fetus was protected from the virilising effects of androgens by aromatisation of the circulating androgens by the placenta. Unlike the related condition, hyperreactio luteinalis, there is a high incidence of masculinisation associated with luteomas of pregnancy. This may reflect the higher concentrations of testosterone seen in this condition but nonetheless is surprising considering the high capacity of the placenta for aromatisation (Hensleigh & Woodruff 1978). There have, however, only been two previous reports of testosterone concentrations in cord blood in histologically defined luteomas, and all of the pregnancies reported were genetically male fetuses (Muechler *et al.* 1987; Baxi *et al.* 1988). This is the first report of umbilical cord concentrations in a case of luteoma with a female fetus; the entirely normal testosterone concentration in the umbilical cord blood suggests that complete aromatisation of the excess maternal testosterone concentration must have occurred to protect the infant. It is possible that previous reports of masculinisation of a female fetus in this condition may reflect abnormalities in the capacity for aromatisation in these cases.

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SHORT COMMUNICATIONS

Outcome of pregnancy following treatment of well-differentiated thyroid cancer with ^{131}iodine

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Well-differentiated thyroid cancer (DTC) accounts for less than 1% of all human cancers, with females outnumbering males by 3:1. More than half of these cancers in women occur in the reproductive years and the prognosis in this group is good (Beenken *et al.* 1989; Tubiana *et al.* 1985). Treatment with radioactive iodine prolongs life even when there are distant metastases (Krishnamurthy & Blahd 1977; Maheswari *et al.* 1981). Children and adolescents treated with ^{131}Iodine for hyperthyroidism and thyroid cancer may later become pregnant (Safa *et al.* 1975; Sarkar *et al.* 1976; Starr *et al.* 1969) but there are insufficient data relating to women of childbearing age presenting with DTC who receive ^{131}I therapy.

Subjects and methods

The case records of 76 women aged between 14 and 45 years seen in the Nuclear Medicine Department of the Royal Liverpool University Hospital (formerly at The Liverpool Clinic) between 1967 and 1990 were reviewed with additional information from their general practitioners. The majority of women were referred by physicians or surgeons for ^{131}I ablation. Other women had already undergone surgery, and were on thyroid suppression therapy with thyroxine 200 μg daily, but continued to attend the clinic at yearly intervals for a clinical examination, thyroid function tests, and serum thyroglobulin estimations. ^{131}I therapy was repeated at six-month intervals until no clinical or imaging evidence of residual or functioning tumour tissue was demonstrable. Thyroid replacement is given between treatments and during yearly follow up. The women are advised not to become pregnant within a year of therapy.

Results

Of the 76 women, none reported miscarriage or infertility problems. Nine women aged between 17 and 37 (mean 23·8) whose follow up period ranged from 2–23 years (mean 13·7) became pregnant five months to seven years after the first ^{131}I therapy (Table 1). All except two women were free of the disease during their pregnancies. There were 15 pregnancies in total.

The women received between 3·7–20·4 GBq (mean 9·7 GBq) ^{131}I. The women who had the stillbirth and the baby with congenital abnormalities had received a total of 7·4 and 8·5 GBq of ^{131}I seven and four years, respectively, before their first pregnancies. One 37 year old woman (case no. 5) became pregnant within five months of receiving 3·7 GBq of ^{131}I and had a normal outcome to the pregnancy. Another woman (case no. 6) had two normal children after three ablation doses of ^{131}I and in the presence of persistent lung metastases.

Four women on thyroid suppression who had never received any ^{131}I also delivered normal babies. Neither the pregnancy nor the thyroid cancer had any adverse effect on each other.

Discussion

Well-differentiated thyroid cancer (DTC) is a condition which predominantly affects women of child-bearing age, and therefore the effect of ^{131}I treatment on future pregnancies needs to be documented. Although radioactive iodine is contra indicated in pregnancy (Drury *et al.* 1984), its beneficial role in prolonging life in DTC with metastasis is well established. However, there is still understandable reluctance to treat young women of reproductive years with ^{131}I for fear of genetic damage despite the absence of any conclusive clinical evidence from humans exposed to therapeutic radiation (Neel & Schull 1956). There have been case reports of normal offspring when ^{131}I was used inadvertantly in the early pregnancy for thyrotoxicosis (Gupta & Garg 1987; Hodges *et al.* 1955).

Sarkar *et al.* (1976) reviewed the subsequent fertility and pregnancy outcome of children and adolescents, both male and female, treated with ^{131}I for thyroid cancer and found no increase in infertility or adverse outcome to pregnancy in his series. However, a review of the literature revealed the paucity of similar data in young women treated with ^{131}I.

All the patients we studied were in the reproductive age group. Out of 15 pregnancies in nine women, 13 were normal. One baby with congenital abnormalities was born to a woman four years after radioactive iodine treatment. After corrective surgery the offspring developed normally. Another patient had a stillbirth as a result of placental insufficiency seven years after ^{131}I therapy. The fact that the same woman who did not receive any further therapy had two children one and two years later makes any possible causative role of radioactive iodine for the stillbirth unlikely.

It was interesting to note that the woman (case no. 5) who became pregnant within five months of therapy with ^{131}I, against advice, delivered a normal, full term baby. The signifi-

Table 1. Details of patients ($n = 9$) who became pregnant after ^{131}I treatment.

Case No.	Age(s) at pregnancy(ies)	Total dose (GBq)	Time since last ^{131}I	Follow up	Outcome of pregnancy
1	29	8·5	17	19	Live birth with VSD and O. atresia
2	23, 26	3·7	23	23	Normal
3	29, 30, 31	7·4	17	17	First stillbirth, others normal
4	31, 32	7·4	15	16	Normal
5	37, 38	3·7	11	11	Normal
6	20, 24	19·7	7	8	Normal
7	29	5·6	6	6	Normal
8	28	20·5	14	22	Normal
9	24	11·2	2	2	Normal

cance of this is further compounded by the fact that this happened at an age (37 years) when pregnancy is considered high risk for chromosomal abnormalities to result in babies (Ferguson-Smith & Yates 1984). Some authors have recommended therapeutic abortion for patients with thyroid cancer who become pregnant (Asteries & Degroot 1976), but the bulk of evidence (Rosvoll & Winship 1965; Hill *et al.* 1966) shows that there is no alteration in tumour growth as a result of pregnancy which proceeds uninterrupted in the presence of coincident cancer. This is exemplified by patient no. 6. Four of our patients had normal pregnancies on thyroxine suppression after surgical treatment for DTC. This supports the evidence that a previous history of thyroid cancer is not enough reason for prevention or termination of pregnancy.

Although our experience over 23 years had yielded only a small number of patients who have become pregnant, it certainly does not raise any alarm for prospective mothers who want to have children after treatment of DTC with radioactive iodine. It has to be stressed, however, that advising these women not to become pregnant within 12 months of ^{131}I therapy is prudent practice.

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Does application of Monsel's solution after loop diathermy excision of the transformation zone reduce post operative discharge? Results of a prospective randomised controlled trial

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Since its initial description by Prendiville *et al.* (1989), loop diathermy excision of the transformation zone has become a common method for the local treatment of colposcopically detected abnormalities of the transformation zone. A number of studies including Luesley *et al.* (1990, 1992), have analysed patient symptoms retrospectively and noted that these were in the main related to vaginal discharge and bleeding of short duration. We report here a prospective study objectively documenting patient bleeding and discharge following loop diathermy. Monsel's solution has been shown to be an effective haemostat at cone biopsy (Gilbert *et al.* 1989); we determined to see if Monsel's solution applied following loop diathermy would reduce vaginal discharge.

Subjects and methods

All consenting patients referred to the academic colposcopy unit were assessed for their eligibility to take part in the study. Exclusion criteria applied to those unlikely to comply with follow up requirements, and to those who were currently in the second half of their menstrual cycle (to avoid menses interfering with assessment of vaginal discharge postoperatively).

The women were randomised at the time of the procedure by sealed opaque envelope to either the control or the Monsel's group. Women in the study underwent diathermy as described by Luesley *et al.* (1990). Where indicated, Monsels' solution was applied by means of a cotton bud to the crater generated. All the women were then instructed to record their daily blood loss for 2 weeks using a sanitary pad chart adapted from Higham *et al.* (1990). The completed charts were returned to the clinic by mail and scored in the manner described by Higham.

Statistics

It was calculated that by entering 60 patients into each arm of the study, there would be a greater than 85% chance of detecting a fall of 25% in the discharge score at the 5% significance level. Results have undergone log transformation where required to correct for positive skewing; differences are expressed using confidence interval (CI) analysis.

Results

Of the 182 women who entered the study, 50 women failed to return their discharge charts, two women suffered primary haemorrhages and five women were found unsuitable for the study after randomisation; these 57 women were excluded from the analysis. The two groups were well matched after randomisation in terms of initial presenting features and size of excision. Application of Monsel's solution did not reduce the quantity or duration of post diathermy discharge (Table 1). Excisions >20 mm in size were significantly more likely to have moderate or severe operative blood loss than those of <20 mm in size (χ^2 16·5, $P = 0{\cdot}0001$). Bleeding was more likely to be present 14 days after the operation in women with larger excisions (odds ratio (OR) 3·5, 95% CI 1·2–9·9). Overall 66% of women were still bleeding on day 14, 20% of whom regarded their loss as moderate or severe (pad score of >20). As a group, women with large excisions had a greater total loss over the 2 week period (difference between means 1·6, 95% CI 0·9–2·3).

Discussion

Haemorrhagic morbidity appears to be closely related to size of the biopsy taken in the same way that haemorrhagic mor-

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Table 1. Size of excision and bleeding characteristics.

	Operator assessment of bleeding at LDE				
Size of excision	Minimal *n*	Moderate or severe *n*	Women bleeding at day 14 (%)	Log of mean total blood loss mean	(SD)
<10 mm	15	0	40	3·001	(0 94)
10–20 mm	56	14	64	3·994	(1 33)
>20 mm	14	18	84	4·572	(1·13)
Monsel's	—	—	64	3.942	(1 3)
No Monsel's	—	—	73	4·14	(1·2)

bidity following cone biopsy is related to size of the excision (Luesley *et al.* 1985). We feel that patient morbidity following loop diathermy excision is underestimated by the use of crude indices, such as re-admission to hospital with secondary haemorrhage; the degree and persistence of vaginal discharge appears to have been generally underestimated in previous retrospective studies (Luesley *et al.* 1990, 1992). It is our opinion that secondary infection of the cervical crater is the responsible pathology behind the high prevalence of prolonged post loop diathermy excision discharge. The use of Monsel's solution does not appear to significantly reduce this discharge and we can not recommend its routine application following diathermy excision.

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BLAIR BELL RESEARCH SOCIETY

Papers presented at the annual general meeting on 27 May 1992 at Royal College of Obstetrics and Gynaecologists, London

Renal haemodynamic reserve during pregnancy in patients with chronic renal insufficiency by S. N. Sturgiss and J. M. Davidson. University Department of Obstetrics and Gynaecology, Princess Mary Maternity Hospital, Newcastle-upon-Tyne.

Although glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), together designated renal haemodynamics, increase during normal pregnancy, an infusion of amino acids will evoke additional renal augmentation indicative of an intact renal haemodynamic reserve (RHR). RHR is evident in pregnant animals with chronic renal disease but to date there are no human data. An amino acid infusion was therefore used to investigate RHR in 12 pregnant women with varying degrees of chronic renal disease. Seven women were studied in both early (12–18 weeks) and late pregnancy (28–34 weeks) and five women in late pregnancy. GFR (mls/min) and ERPF (mls/min) were determined by infusions of insulin and para-aminohippurate (PAH), respectively, measured as a mean of three 30 min clearance intervals before and after an infusion of Vamin 9 (Kabi Pharmacia); this provides 60 g of first class protein and is infused at a rate of 4 mls/min for 210 mins. Mean GFR did not significantly increase during the amino acid infusion in early pregnancy but increments of more than 10 mls were evident in two women. In the seven women studied serially, amino acid infusions in late pregnancy evoked a significant ($P<0{\cdot}05$) increase in ERPF (531 [77] versus 608 [88] mls/min), but GFR remained unchanged. The failure of GRF and ERPF to increase during early pregnancy indicate an attenuation of RHR. Individual responses were, however, variable with some women responding in a comparable fashion to that observed in normal pregnancy. The RHR observed in late pregnancy may have been the effect of decrements in basal haemodynamics. The study is being continued in order to determine the prognostic value of RHR in early pregnancy and to compare puerperal values with those observed during pregnancy.

The functional response of the cervix in the first stage of labour by K. S. Olah and H. Gee. Department of Fetal Medicine, Birmingham Maternity Hospital, Birmingham.

A prospective study was conducted to analyse the response of the cervix to myometrial contractions in labour. Intrauterine pressure and cervical dilatation were continuously recorded in 48 women requiring oxytocin stimulation of labour. All the analogue signals were digitally converted and stored on disc for later off-line analysis. The rate of rise of pressure (dp/dt), change in cervical dilatation (dc/dt) and a compliance index (CI) defined as (dp/dt)/(dc/dt) were recorded. Residual dilatation correlated with dc/dt ($R=0{\cdot}89$) and was negatively correlated with CI ($r=-0{\cdot}69$). There was no correlation between residual dilatation and dp/dt ($r=-0{\cdot}16$). In 18 women contractions of the cervix were observed in early labour at a dilatation of 2 to 4 cm with a mean amplitude of 0·3 cm (range 0·16–0·61 cm). It has been suggested that a compliant cervix will down modulate uterine wall tension resulting in a lower dp/dt and lower generating pressures. This has been termed the cervical augmentation/attenuation of pressure (CAP) effect. The above data support this hypothesis. The change in response of the cervix during labour from active contractions to passive dilatation may reflect the changing function of the cervix. The contractions would effect cervical compliance and this has implications for the clinical management of the latent phase of labour.

Cytokine production by cervical carcinoma cell lines: autocrine growth effects by D. Eustace*, X. Han**, R. Gooding***, A. Rowbottom*** and E. Heyderman**. Departments of Obstetrics and Gynaecology* and Histopathology**, St. Thomas' Hospital, London and the Department of Immunology***, Westminster Hospital Medical School, London.

The concentration of interleukin-1 α and β, interferon δ, tumour necrosis factor α and β, and interleukin-6 were

Table 1. Renal haemodynamic reserve. Values are given as mean (SE) (Sturgiss & Davidson)

		Pre-infusion		Post-infusion		Change (%)	
Gestation	*n*	GFR	ERPF	GFR	ERPF	GFR	ERPF
Early	7	93 (37)	601 (99)	96 (36)	632 (97)	3.2	5.2
Late	12	80 (14)	449 (75)	86 (15)	521 (84)	7.4	16.0

measured in the supernatant from cultures of the novel cervical carcinoma cell lines XH1, EH2, JE6 and SM7 and from established cell lines A431 and Caski. The supernatant were analysed by ELISA or RIA techniques. All the cell lines were found to secrete interleukin-6 with maximum production rates of 100 pg/mml to 11 mg/ml. None of the cell lines produced significant quantities of the other measured cytokines. The interleukin-6 produced by the cervical cell lines was biologically active on the basis of a bioassay dependent upon interleukin-6 dependent growth of the B9 hybridoma cell line. The possible role of interleukin-6 as an autocrine growth factor for carcinoma cell lines was investigated using goat anti-human interleukin-6 neutralising polyclonal antibody. Inhibition of the growth of the cell lines XH1, EH2, JE6, SM7 and Caski was seen *in vitro*, whilst the growth of A431 was unaffected. The degree of inhibition was maximal at antibody dilutions of 1:50. Interleukin-6 appears to function as an autocrine growth factor in cervical carcinoma.

The role of free radical activity in ovarian cancer by C. R. Taggart, O. J. Owens, R. Wilson and J. J. Walker. University Departments of Medicine and Obstetrics and Gynaecology, Glasgow Royal Infirmary, Glasgow.

Free radicals have been implicated in the aetiology and progress of malignant disease as well as in the response of tumour to treatment. We have studied the role of free radicals in benign, borderline and malignant ovarian tumours compared to an aged-matched control group. We have measured five parameters of free radical activity, plasma thiol, red cell lysate thiol, glutathione, caeruloplasmin and superoxide dismutase, before and after surgery in 34 women with ovarian tumours. These consisted of 16 benign, 15 malignant and 3 borderline tumours. Plasma thiol was significantly reduced in the malignant group compared with controls (325 [19] versus 438 [85] µmol/l, $P<0{\cdot}03$). Lysate thiol was reduced in the benign group compared to controls (345 [164] versus 507 [222] µmol/l, $P<0{\cdot}01$). The results suggest that women with ovarian cancer have alterations in the reduction/oxidation balance across the red cell membrane making the cells more susceptible to free radical attack. Further work is needed to assess the effects of treatment and tumour recurrence on free radical activity in patients with malignant ovarian tumours.

The renin–angiotensin–aldosterone and atrial natriuretic peptide responses to volume expansion in normal pregnancy by D. L. Bisson, D. Hampton*, G. D. Dunster, J. P. O'Hare and F. Broughton-Pipkin**. Royal United Hospital, Bath, Royal Gwent Hospital, Newport*, Queen's Medical Centre, Nottingham**.

Normal pregnancy is associated with an increased plasma volume, increased activity of the renin–angiotensin–aldosterone system (RRA) and elevation of atrial natriuretic peptide (ANP). To test the hypothesis that the RAA and ANP respond appropriately around the new elevated baselines, the renal and hormonal response to volume expansion during pregnancy and postpartum in the same subjects were studied. The responses to volume expansion produced by head-out water immersion (HOWI) in 16 normal women at 34 weeks gestation and postpartum were compared. There was a two-fold increase in diuresis, natriuresis and increase in ANP with a 70% suppression of plasma aldosterone (PA) to HOWI which was similar in pregnancy to the puerperium. Despite an elevated baseline, pregnancy was associated with a reduced percentage suppression of plasma renin concentration (PRC) compared with postnatally ($P<0{\cdot}05$ ANOVA) and a suppression of plasma renin substrate (PRS) which was not seen postnatally ($P<0{\cdot}05$, ANOVA). The renal response to HOWI was similar in pregnancy and postnatally. Despite an elevation of basal levels, the stimulating of ANP and suppression of PA were identical. However, pregnancy is associated with a reduced suppression of PRC and an increased suppression of PRS during volume expansion which may reflect alterations in their sensitivity in pregnancy and which suggests that the RAA is not simply reset around a higher baseline.

The inhibition of contractions of the isolated human myometrium by potassium channel openers by J. M. S. Cheuk, M. Hollingsworth and M. J. A. Maresh. Smooth Muscle Research Group, Departments of Physiological Science and St. Mary's Hospital, Manchester.

Potassium channel openers (KCOs) are a novel class of smooth muscle relaxants which are potent uterine relaxants in the rat. The relaxant properties of two prototype KCOs, aprikalim and BRL 38227, were studied in isolated human myometrium. Samples were collected from the lower uterine segment during caesarean section at term and from the body of the uterus after hysterectomy. The effects of the KCOs on both potassium chloride and oxytocin induced contractions were studied in organ bath experiments. The antagonism by the ATP-dependent potassium channel blocker, glibenclamide, was also assessed. At concentrations of both 1 µmol and 10 µmol aprikalim and BRL 38227 suppressed contractions to low (<40 mmol) but not high (>40 mmol) potassium chloride induced contractions, an action consistent with potassium channel opening. Both drugs inhibited phasic contractions induced by oxytocinon (1nmol) with a mean pD_2 of 6·61 and 6·79, respectively, in the pregnant group, and 7·21 and 7·41, respectively, in the non-pregnant group. Both drugs were significantly more potent in myometrium from non-pregnant than pregnant women. Glibenclamide (1 µmol) antagonised both drugs in both groups, suggesting that they act via glibenclamide sensitive potassium channels. It is concluded that KCOs are potent relaxants of isolated human myometrium and may have therapeutic potential in preterm labour and dysmenorrhoea. Further studies are necessary to assess their tissue selectivity and their effects at earlier gestation.

Bovine collagen implants in the management of recurrent genuine stress incontinence after failed surgery by S. Eckford and P. H. Abrams. Department of Urodynamics, Southmead Hospital, Bristol.

The best chance of success when treating women with genuine stress incontinence (GSI) is at the first operation. Failed procedures provide considerable management difficulties. Over a 15 month period a group of 46 women with recurrent post-operative, urodynamically proven GSI were studied. They had previously undergone 1 to 4 operations, 36 having had 1 or 2 operations and ten 3 to 4 operations. As a day case procedure under local anaesthetic, glutaraldehyde cross-linked collagen was injected para-urethrally around the bladder neck under cystoscopic control. Follow-up at 1 month by subjective and objective testing was performed. A second injection was offered to those not rendered completely continent. Three months post-completion of treatment subjective and urodynamic testing was repeated. Forty-one (89%) of women were subjectively cured at 3 months, falling to 30 (80%) at 6 months. Complications were minor with only one woman being unable to tolerate the procedure under regional anaesthesia. When compared with a group of 30 women who had para-urethral collagen implantation as first line treatment for their GSI those with previously failed surgery faired significantly better. In conclusion, this simple day case procedure of para-urethral collagen implantation has a role to play in the management of women with failed previous incontinence surgery.

Predictive value of parameters of urethral function in the investigation of women with genuine stress incontinence by D. P. Keane, S. D. Eckford and P. Abrams. Department of urodynamics, Southmead Hospital, Bristol.

The urethral pressure profile (UPP) at rest and during stress has been the most widely used adjunct to cystometry in the prediction of women with genuine stress incontinence (GSI). However, the value of the UPP has been questioned recently (Versi *et al.* 1986). The present study was designed to determine which functional urethral parameters, either alone or in combination, could be used to preduct GSI. Three hundred-thirty nine premenopausal women were studied by videourodynamics, including provocative cystometry and a UPP performed at rest as well as during stress. Two hundred-eighty eight women had GSI and 51 were stress continent. The stress UPP had a high specificity (100%) but a low sensitivity (38%), but whereas a negative (abnormal) profile had a high predicative value (100%), a normal stress profile had a positive predicative value of 35%. There were significant differences in the values for maximum urethral closure pressure (MUCP), pressure transmission ratio (PTR) and functional urethral length (FUL) between the continent and incontinent groups. A multivariate discriminant analysis of these parameters ranked MUCP as the most important predictor of continence followed by the stress UPP and PTR. The FUL was not independently significant. The analysis provided cut-off values for all these parameters in the prediction of GSI. Using these cut off points, GSI could be predicted with a high probability ratio but there was no parameter of urethral function alone, or in combination which yielded a high probability rate for predicting continence.

Table 2. Estimated fetal weight (Keane, Ekford & Abrams).

	Gestation (weeks)		
Ethnic population	28	32	36
Caucasians			
Mean	1259	2012	2863
95% CI*	1206–1292	1954–2070	2782–2946
Bangladeshi			
Mean	1098**	1719**	2539**
95% CI*	1007–1198	1614–1830	2369–2720

*CI=confidence interval, **$P<0{\cdot}01$ (T-test).

Reference

Versi, E., Cardozo, L., Studd, J. & Cooper, D. (1986) Evaluation of urethral pressure profilometry for the diagnosis of genuine stress incontinence *World J Urol* **4**, 6–9

The endometrial leucocytes in infertile women by L. D. Klentzeris, J. N. Bulmer, A. Warren, T. C. Li and I. D. Cooke. Harris Birthright Research Centre, Sheffield.

In order to determine whether the endometrium of women with unexplained infertility differs from the endometrium of women of proven fertility, a panel of 11 monoclonal antibodies was used to characterise the endometrial leucocyte population. Precisely timed endometrial biopsies were obtained from 24 fertile women (Group 1) and from 24 women suffering from unexplained infertility (Group 2). Frozen sections were labelled using an avidin–biotin peroxidase method and leucocyte subsets were quantified using a Quantimet 970 image analyser. Seven days after the luteinising hormone surge (LH+7), Group 1 had a higher concentration of CD8+ (T suppressor/cytotoxic cells in comparison with Group 2 ($P<0{\cdot}001$). In contrast, the number of CD4+ (T helper/inducer) cells was significantly higher in Group 2 particularly 13 days after the LH surge ($P<0{\cdot}01$). In normal fertile women endometrial granulated lymphocytes (CD56+, CD2+, CD38+, CD3−) increased from day LH+4 with most (80%) of the increase occurring between days LH+7 and LH+13. On day LH+7, CD56+ cells accounted for 51% of the endometrial leucocytes and by LH+13 this has risen to 59%. Throughout the luteal phase Group 2 had fewer CD56+ cells than Group 1. These results indicate differences in leucocyte subsets in fertile compared with infertile women. Endometrial leucocytes may contribute to unexplained infertility, possible by affecting the embryo–maternal dialogue during the implantation phase.

Sensitivity of feto-placental arteries to U46619 by A. L. McCarthy, K. S. Raju and L. Poston. St. Thomas's Campus, London.

The control of feto-placental blood flow is poorly understood, though locally produced vasoactive factors are likely to play a major role in view of the absence of an autonomic nerve supply. Such factors may originate in the intravascular space, such as thromboxane released from activated platelets, or from arteries such as endothelium derived relaxing factor. In this study the sensitivity of feto-placental arteries to U46619, a thromboxane analogue, was examined and corre-

Table 3. Vaginal ultrasound in early pregnancy (Chang *et al.*).

Time intervals	Chorionic sac *n*	Yolk sac *n* (%)	Fetal pole *n* (%)	Heart beat *n* (%)	Amniotic membrane *n* (%)	Midgut hernia *n* (%)
Days post-conception						
18–20	4	3 (75)	0	0	0	0
21–23	13	11 (85)	1 (8)	0	0	0
24–26	10	9 (90)	8 (80)	2 (20)	0	0
27–29	15	15 (100)	15 (110)	15 (100)	0	0
30–32	15	15 (100)	15 (100)	15 (100)	3 (20)	0
33–35	16	16 (100)	16 (100)	16 (100)	10 (63)	0
36–38	15	15 (100)	15 (100)	15 (100)	13 (87)	0
39–41	14	14 (100)	14 (100)	14 (100)	14 (100)	0
Weeks post-conception						
6	39	39 (100)	39 (100)	39 (100)	39 (100)	13 (33)
7	42	42 (100)	42 (100)	42 (100)	42 (100)	39 (93)
8	43	43 (100)	43 (100)	43 (100)	43 (100)	38 (88)
9	41	36 (88)	41 (100)	41 (100)	33 (80)	16 (39)
10	36	14 (39)	36 (100)	36 (100)	19 (53)	0
11	39	3 (8)	39 (100)	39 (100)	14 (36)	0
12	41	0	41 (100)	41 (100)	5 (12)	0

lated to artery diameter. Placental biopsies were taken within 10 min of delivery and placed in cold physiological salt solution. Branches of the main stem villous were then dissected under magnification providing 54 specimens with a mean normalised internal diamter of 380 μm (range 163–646). The arteries were mounted on a small vessel myograph (Mulvaney/Halpen) and stretched to mimic a transmural pressure of 37 mmHg. The sensitivity to U46619 (10^{-10} to 10^{-6}) was examined in the presence of 5% carbon dioxide in nitrogen. In this low oxygen environment U4619 elicited a dose-dependent increase in tone with a mean (SEM) maximum tension of 3·85 (0·26) mN/mm of artery length at 10^{-6} mol, with a mean EC_{50} of 1·45 × 10^{8} mol. There was no correlation of EC_{50} with vessel diameter. U46619 is a potent vasoconstrictor in the feto-placental vascular bed. Platelet activation and thromboxane A^2 released in this circulation may therefore have detrimental effects on feto-placental bloodflow. This could be of importance in pregnancies complicated by abnormal umbilical Doppler waveforms.

Fetal growth: a comparison between Bangladeshi and Caucasian women by T. C. Chang, S. C. Robson, J. A. D. Spencer and S. Gallivan. University College Hospital and University College, London.

Bangladeshi women are known to have smaller babies than Caucasian women. A high proportion of such babies are classified as being small for gestational age when Caucasian standards are used. Although a number of cross sectional studies have reported ultrasonic measurements, fetal growth curves derived from serial data have not previously been reported for Bangladeshi women living in the United Kingdom. Serial measurements of biparietal diameter, head and abdominal circumference and femur length were performed on 20 Bangladeshi and 67 Caucasian fetuses at 20 weeks gestation and then fortnightly from 26 weeks until birth. Gestational age, as determined from the intial scan, was within 7 days of the postmenstrual age in all cases. Estimated fetal weight (EFW) was calculated using a standard formula, and individual growth curves were then derived. The mean EFW was compared between the two populations at 28, 32 and 36 weeks gestation (see table). In conclusion, fetuses of Bangladeshi women have a different growth profile compared with Caucasian fetuses. Optimal interpretation of fetal growth necessitates the use of charts appropriate to ethnic groups.

Gestational development markers assessed by vaginal ultrasound by M. S. Mills, D. K. James and M. G. R. Hull. University Department of Obstetrics and Gynaecology, St. Michaels Hospital, Bristol.

A longitudinal study of developmental markers in 45 human fetuses with known dates of conception was carried out by transvaginal sonography. The presence of the yolk sac, fetal pole, heart beat, amniotic membrane and midgut hernia were noted (see table). This study defined structural changes seen by vaginal sonography which will be useful in the assessment of first trimester pregnancies.

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CORRESPONDENCE

Audit in gynaecology

Sir,

I read with interest the commentary by Professor Chamberlain in the March 1992 issue of the *Journal* about audit in gynaecology and the difficulty of data collection and the organisation of gynaecological audit meetings.

I have just been attempting to audit the medical management of endometriosis and fully support his views. The most difficult part of this audit was the data collection. The regional computer centre was contacted by our audit co-ordinator and the data provided were analysed based upon the names of women who were diagnosed to have endometriosis within the preceding year. The data suggested there were 87 patients; 25 had endometriosis but of the rest, 25 had adenomyosis, 6 had endometritis and 9 women had pelvic pain with no pathology found.

I attempted to use the drug prescriptions to obtain a list of women who had used drugs for symptomatic treatment of endometriosis. However, the pharmacy did not have a computerised record of women who were prescribed danazol, provera, or the GnRh analogues. The only way to collect the data was to go manually through all the prescriptions written for outpatients throughout the hospital for twelve months in order to collect the names of the women who were prescribed any of the above drugs. This took two doctors more than ten hours.

This hospital uses a system of remote patient activity, which is located and managed by regional headquarters. At present it is only coding inpatient activity, such as gynaecological operations. Diagnostic codes are added by the coders at the regional health authority (Bunch 1992). The result is inadequate and inappropriate data retrieval for any clinical purpose such as clinical audit meetings. This audit did, however, help to uncover the insufficient and poor nature of the data storage on certain topics of gynaecology such as endometriosis and pelvic inflammatory disease.

It may be possible to collect accurate clinical data without spending a lot of money provided managers can be persuaded that the primary function of a clinical information system is to collect clinical data, to improve the clinical services, and to assist with clinical audit (Smith 1992).

Arrangements are now being made for improvements in the coding system for the regional computer centre and the pharmacy has now agreed to keep a computerised record of women who have been prescribed danazol or one of the GnRh analogues for endometriosis. I wonder if any one else has had a similar or better experience of audit in gynaecology on such conditions in which diagnosis, findings and treatment are so varied and in which poorly kept records are frequently encountered.

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Immunohistochemistry in pelvic nodes of patients with cervical cancer

Sir,

We were interested to read the short communication from Gitsch *et al.* (1992) in which they were unable to identify any micrometastases by immunohistochemistry in the lymph nodes of 10 patients with early stage cervical cancer who later developed recurrence. We performed a similar study on three patients with early (<1 year) recurrence after radical hysterectomy for stage 1B and 2A cervical cancer in which the nodes had all been negative by conventional examination. The primary tumours, and 10, 13 and 14 nodes respectively, were re-examined using the monoclonal antibody CAM 5·2 and an indirect peroxidase technique. All three primaries were positive but no mircrometastases were identified. We also re-examined the nodes from five patients without early recurrence but again found no micrometastases We agree that immunohistochemistry is unlikely to be an improvement on routine histology for the diagnosis of micrometastases in cervical cancer

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BOOK REVIEWS

Doppler Ultrasound in Perinatal Medicine, edited by J. Malcolm Pearce. Oxford University Press, Oxford, New York, 1992. 364 pages, with figures and tables £50.00.

This book should be subtitled, 'Everything You Wanted to Know About Doppler Ultrasound but were Afraid to Ask' It is a well thought out, well written book, edited by the ultimate Doppler enthusiast who begins with two excellent chapters on the basic considerations—the first on the physics of Doppler ultrasound and the second on statistics as applied to Doppler ultrasound studies

The second chapter is an extremely good idea as it helps make the book compulsory reading for any researcher wanting to do studies in this area. The book basically demonstrates what is possible with the use of Doppler ultrasound in perinatal medicine. It points out the limitations and what we would expect from the use of Doppler and its role in monitoring various patient groups. It tells the reader which particular arteries will show changes in which particular groups and therefore what to do to whom. The book concentrates on fetal and uteroplacental Doppler and I think that the addition on the management of fetal dysrhythmia is helpful to follow on the use of Doppler in this diagnosis. There is a complementary chapter on neonatal cerebral blood flow and a single chapter on assessment of maternal cardiac output. It does not mention the use of Doppler in the assessment and diagnosis of DVT in pregnancy.

The chapters are well written by the people who have done the work. It reads like a 'Who's Who?' of Doppler ultrasound, although there is an inevitable London bias, many of whom have a connection, past or present, with King's College Hospital The authors are recognized international authorities in this area and they are all enthusiasts of the techniques and therefore there is an undoubted bias towards the role of Doppler ultrasound, so do not buy this book to look for any scepticism of ultrasound's role.

This book would be invaluable for any obstetrician or radiologist in training and should be part of any obstetric library and is compulsive reading for anyone attempting to carry out research in Doppler ultrasound in perinatology. It would also be useful to read prior to the purchase of any ultrasound machine so that the reader would know what value it may have and which particular equipment one should buy.

In summary, this is a well written, well designed textbook which I would strongly recommend.

James J. Walker

The Stress of Multiple Births edited by David Harvey & Elizabeth Bryan. 140 pages, illustrated. £15.00 (£12.00 to members of the MBF).

This book is a compilation of papers arising from a workshop of the same name held in December 1989 It draws together results from much of the recent literature with the aim of recognising the special problems faced by the families of multiple births, their medical attendants, and the children themselves. It brings together papers dealing with the very different problems experienced at each stage from the obstetric viewpoint antenatally, through to the perception of twins themselves growing up as twins. Throughout the book there is a good balance between medicine, its application, and the very different social situation these families find themselves in. It updates the previous literature although it contains little that is new. Its appeal is in its realistic presentation of the issues that have to be considered throughout the overwhelming and costly task of rearing a multiple birth family. It is enhanced by those sections written from first-hand experience

I would recommend this as a useful book for clinicians and those working in the social services, particularly for those new to the field of multiple births. It raises the various complex issues which need to be addressed individually for each multiple birth. I reiterate the hope given at the end of the Preface that the discussions and consequent resolutions given at the end of the book will help professionals to recognise the special problems faced by multiple births and their families.

Beverley Botting

Women's Health Matters edited by Helen Roberts. Routledge, London and New York, 1992, 200 pages, £10.99.

'Sufficiently exciting to act as a real incentive to those starting to think about doing their own research', this lively book presents ten individual projects on women's health in the childbearing years, as a way of looking at the complexities of qualitative sociological research conducted by women for women. A sister volume is entitled Women's Health Counts (Roberts, Routledge 1990) The practical challenges of raising funds, selecting and setting up the most appropriate research design, and considering the ethics, become stimulating topics in themselves. The contributors, all experienced in their different fields of public health, nursing and the social sciences, seem to speak with one voice. Whether exposing shortcomings of research into black women's health, gender differences in reporting ill health, the effects of chronic tiredness, women's need to 'cope', the stresses of caring for triplets, quadruplets and more . . . the shared aim is to explore experiences from the women's perspective. Refusing to be bound by narrow hypotheses, but rather taking note of the subjective reality of daily life—and not omitting to acknowledge women's contribution as active collaborators rather than passive statistical objects—the researchers appear to reach a broadened understanding. Whilst firmly, yet on the whole unprovocatively feminist, they keep in mind differences in gender, class, race and culture. They emphasise that social research, inherently part of the social world it studies, may give support to those being studied, and thus in itself affects the behaviour it seeks to explain.

Decidedly a book to acquire and dip into: one can here only offer the smallest glimpse and hope to whet the appetite for more.

Fay Amias

Books received some of which may be reviewed at a later date:

Gynaecology edited by J. Rymer, A. N J. Fish & M. Chapman. Churchill Livingstone, Edinburgh, 1992. 122 pages with figures and tables, £7.95

Health Care for Older Women edited by Julie George & Shah Ebrahim. Oxford University Press, Corby, 1992. 267 pages with figures and tables, £25.00

High Risk Pregnancy edited by A. A. Calder & W Dunlop. Butterworth-Heinemann, Oxford, 1992. 447 pages with figures and tables, £60.00.

International Nomenclature of Disease—Volume III. Diseases of the Female Genital System edited by the World Health Organization. World Health Organization Publications, Switzerland, 1992. 126 pages, Swiss Francs 23/US$ 20 70.

Lecture Notes on Obstetrics edited by Geoffrey Chamberlain and J Malcolm Pearce. Blackwell Scientific, Oxford, 1992. 288 pages with figures and tables, £12.95.

Prostaglandins and the Uterus edited by J. O. Drife & A. A. Calder Spring-Verlag, Berlin, 1992. 301 pages with figures and tables, DM 228.00.

Surgical Repair of Vaginal Defects edited by Wayne F Baden and Tom Walker. J. B Lippincott Company, Philadelphia, 1992. 294 pages with figures and tables, £75.00

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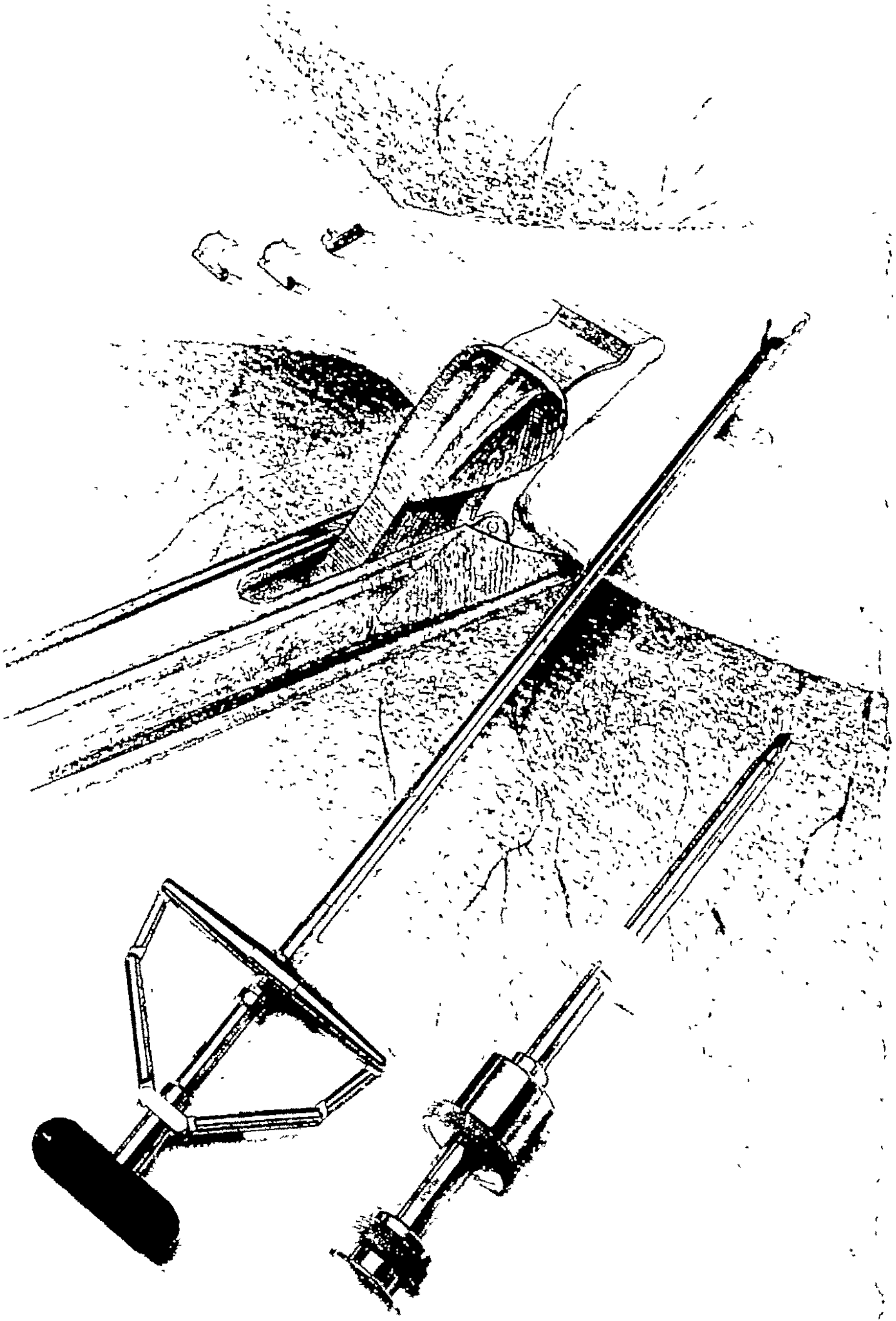
Simple, reliable female sterilisation.



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(1) Toplis PJ et al, Brit J Family Planning 14 43–45, 1988

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